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**Poster**

**PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.01/A1

**Topic:** A.01. Neurogenesis and Gliogenesis

**Title:** Exploring adult hippocampal neurogenesis in the common marmoset

**Authors:** \*S. ENRIGHT<sup>1</sup>, S. L. PARYLAK<sup>2</sup>, F. H. GAGE<sup>3</sup>, J. C. MARTINEZ-TRUJILLO<sup>4</sup>;  
<sup>1</sup>Univ. of Western Ontario, London, ON, Canada; <sup>2</sup>LOG-G, Salk Inst., La Jolla, CA; <sup>3</sup>LOG-G, Salk Inst. for Biol. Studies, La Jolla, CA; <sup>4</sup>Dept. of Physiol. and Pharmacol. and Psychiatry, Western Univ., London, ON, Canada

**Abstract:** Adult hippocampal neurogenesis (AHN) has been extensively reported in rodents, with several studies documenting the developmental and maturation processes of adult-born cells. In mammals, AHN occurs in the dentate gyrus (DG) and has been implicated in learning, memory, and other hippocampal-specific processes. However, studies have reported that AHN seems to present at lower levels in humans, and neurogenic rates are widely disputed. Additional research analyzing AHN in non-human primate (NHP) models is necessary to further understand species-specific differences to effectively translate this knowledge to humans. Here, we use dual labelling with bromodeoxyuridine (BrdU) and ethynyl deoxyuridine (EdU) to quantify AHN and explore survival rates of adult-born neurons in a small primate, the common marmoset (*Callithrix jacchus*). Our results show several adult-born neurons within the subgranular zone (SGZ) of the DG. These cells express neuronal markers and differ from proliferating glial cells, demonstrating distinct neurogenesis in the marmoset. Neurogenic rates differ between mice and marmosets, suggesting differences in AHN are likely related to the species' lifespan and may be an evolutionary adaptation to optimize stability in neuroplasticity. We also explore novel methods to examine morphological distinctions between adult-born neurons of non-human primates (NHPs) and rodents, as well as the resulting impacts on circuits and behaviour. We propose that the common marmoset may serve as an essential intermediate model to translate data from rodent models to human studies, providing insight into neuropsychiatric and neurodegenerative disorders that affect AHN and memory.

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**Poster**

**PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.02/A2

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** ICMR-10595/2021

**Title:** Hilum of the dentate gyrus: An overlooked site for continued neurogenesis in human adults

**Authors:** \*A. KUMAR<sup>1</sup>, S. PAIKRA<sup>2</sup>, R. KUMAR<sup>4</sup>, P. KUMAR<sup>5</sup>, A. K. RASTOGI<sup>2</sup>, A. K. DATUSALIA<sup>6</sup>, C. KUMARI<sup>7</sup>, A. ASGHAR<sup>3</sup>;

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**Abstract: Background:** The sub-granular zone (SGZ) of the dentate gyrus (DG) part of the hippocampus is a known active site for continued neurogenesis in adult humans. Although, often indicated in animal studies, the hilum of the dentate gyrus is not well studied in humans. **Methods:** We performed immunohistological examination of 30 postmortem specimens of human hippocampus using a neurogenesis panel of markers. In addition, morphological characterization of cells in the hilum of DG were performed using routine Hematoxylin and Eosin (H&E) and special neuronal stains (Nissl's and modified Golgi-Cox). **Results:** The cell population was scarce in the hilum compared to the SGZ. However, the neural and glial lineage cells were found dispersed across the hilum, including the progenitor cells. Uniquely, a sub-population of DCX<sup>+</sup> PSA-NCAM<sup>+</sup> large, multipolar cells were visible. The morphological characteristics of these matched with the previously described mossy cells in the hilum. **Conclusion:** The hilum of the DG presents to be an additional site for continued neurogenesis in adult humans. The neurogenic population of hilum is distinct from that in SGZ and may have specific roles in reorganization of hippocampal circuitry, that needs to be further investigated.

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**Poster**

**PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.03/A3

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** The Swedish Research Council  
ERC (ERC-2015-AdG-695096)  
Swedish Cancer Foundation

Knut och Alice Wallenbergs Stiftelse  
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**Title:** Identification of proliferating neural progenitors in the adult human hippocampus

**Authors:** \*I. G. DUMITRU, M. PATERLINI, J. FRISEN;  
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**Abstract:** Continuous adult hippocampal neurogenesis is involved in memory formation and mood regulation but is challenging to study in humans. Difficulties finding proliferating progenitor cells questioned if and how new neurons may be generated. Here we analyzed the human hippocampus from birth through adulthood by single nucleus RNA-sequencing. We identified all neural progenitor cell stages in early childhood. In adults, using antibodies against the proliferation marker Ki67 and machine learning algorithms, we found proliferating neural progenitor cells. Furthermore, transcriptomic data showed that neural progenitors were localized within the dentate gyrus. The results contribute to understanding neurogenesis in adult humans.

**Disclosures:** I.G. Dumitru: A. Employment/Salary (full or part-time): AAX Biotech AB. M. Paterlini: None. J. Frisen: None.

## Poster

### PSTR199: Postnatal Neurogenesis

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.04/A4

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NRF of Korea 2018R1A5A2025964  
NRF of Korea 2020R1A2C1014372  
NRF of Korea RS-2024-00509757  
KHIDI RS-2023-00262321

**Title:** Dkk2 contributes to pattern separation and adult hippocampal neurogenesis by suppressing Wnt/PCP signaling

**Authors:** W. SONG<sup>1</sup>, L. JAE MIN<sup>2</sup>, S. YOON<sup>4</sup>, \*M.-H. KIM<sup>3</sup>;  
<sup>1</sup>Physiol., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; <sup>2</sup>Seoul Natl. Univ. Col. of Med., Seoul / Jeong-ro, Korea, Republic of; <sup>3</sup>Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; <sup>4</sup>Anat. and Neurobio., Univ. of California Irvine, Irvine, CA

**Abstract:** Wnt signaling plays a pivotal role in normal brain development and function. Dickkopf-related protein 2 (DKK2), a member of the DKK family (DKK1–4) proteins, modulates Wnt signaling either positively or negatively by interacting with WNT co-receptors low-density lipoprotein receptor-related proteins 5 and 6 (Lrp5/6). However, the role of DKK2 in



the brain remains elusive. Here, we demonstrated that DKK2-mediated suppression of Wnt signaling is essential for hippocampal function. *Dkk2*<sup>+/-</sup> mice exhibited impaired pattern separation and reduced adult hippocampal neurogenesis (AHN). Genetic disruption of *Dkk2* (*Dkk2*<sup>+/-</sup> and *Dkk2*<sup>-/-</sup>) and chronic DKK2 administration into the brain affected AHN bidirectionally. Furthermore, homozygous and heterozygous *Dkk2* deletions exerted differential effects on the Wnt signaling pathway in the hippocampus. Complete loss of *Dkk2* enhanced both Wnt/ $\beta$ -catenin and Wnt/planar cell polarity (PCP) signaling, while haploinsufficiency of *Dkk2* mainly enhanced the activity of the Wnt/PCP signaling pathway. In hippocampal slices, DKK2 suppressed Wnt3a- and Wnt5a-mediated activation of Wnt/ $\beta$ -catenin and Wnt/PCP signaling, respectively. Chronic suppression of c-Jun N-terminal kinase signaling reversed the attenuated neurogenesis and impaired pattern separation observed in *Dkk2*<sup>+/-</sup> mice. Collectively, these results suggest that DKK2 is a negative regulator of Wnt signaling but promotes AHN, and suppression of Wnt/PCP signaling could promote AHN.

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## **Poster**

### **PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.05/A5

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NIH Grant NS078294  
NIH Grant P50HD103555

**Title:** Mef2c as an important regulator of adult-born neuron survival and activity-dependent development in the mouse olfactory bulb

**Authors:** S. BAO<sup>1,2</sup>, Y. QI<sup>1</sup>, G. QI<sup>1,2</sup>, Z. ZUO<sup>1</sup>, H. CHEN<sup>1,2</sup>, J. LI<sup>1</sup>, E. K. TANTRY<sup>1,2</sup>, A. INSALACO<sup>2,1</sup>, S. B. HANNAN<sup>1,2</sup>, H. LI<sup>1</sup>, \*B. R. ARENKIEL<sup>1,2</sup>;  
<sup>1</sup>Baylor Col. of Med., Houston, TX; <sup>2</sup>Jan and Dan Duncan Neurolog. Res. Inst., Houston, TX

**Abstract:** Adult neurogenesis is a highly plastic process where adult-born neuron (ABN) development and circuit integration are tuned by sensory input. However, which transcription factors (TFs) couple neural activity to the large-scale gene-expression programs that govern ABN survival and development remains unknown. The mouse olfactory bulb (OB) provides an excellent model, owing to the high plasticity and experimental accessibility, to elucidate the mechanisms that govern ABN neural circuit integration. Our previous single-cell RNA-sequencing data (Tepe et al., 2018) identified MEF2C, a member of the activity-dependent MEF2 family TFs, as a candidate to guide ABN development. Using EdU birth-dating, we found that MEF2C is up-regulated concurrently with the ABN activity-dependent critical period. Through stereotaxic injection of AAV-Cre for conditional loss of function in *Mef2c*<sup>fl/fl</sup> mice, we observed that MEF2C is required for proper ABN integration and survival. To probe the

underlying mechanisms that govern this process, we performed single-nucleus multiome (simultaneous RNA + ATAC) sequencing on ABNs enriched by nuclei-sorting from *Mef2c* KO and WT mice at time points spanning the critical period (harvested at varying intervals following tamoxifen induction of *Dlx1/2-CreERT2*; *CAG-Sun1-sfGFP*; with or without *Mef2c*<sup>fl/fl</sup>). Differential abundance analysis revealed that Calb2<sup>+</sup> periglomerular cells were the most susceptible subtype to MEF2C loss, with their proportion dropping from 8.9 ± 0.6% in WT to 5.8 ± 0.6% in KO. Differential gene expression and ontology analysis further uncovered dysregulation of mitochondrial, cytoskeletal, and synapse organization/signaling pathways. Consistently, enhancer-driven regulon analysis using the SCENIC+ package revealed that MEF2C acts strongly in granule cells and Calb2<sup>+</sup> periglomerular cells to regulate chromatin regions and genes involved in cytoskeletal remodeling, synaptic plasticity, and survival. Together, these findings support that MEF2C is an important TF that orchestrates epigenetic and transcriptional programs for activity-dependent ABN development during the critical period, and supports ABN survival. In the long term, harnessing MEF2C via inducible overexpression or activation may illuminate strategies for brain repair by tuning synaptic integration and enhancing neuronal survival.

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## Poster

### PSTR199: Postnatal Neurogenesis

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.06/A6

**Topic:** A.01. Neurogenesis and Gliogenesis

**Title:** Elucidating the Role of Adult Hippocampal Neurogenesis Dietary Restriction-induced Memory Enhancement

**Authors:** \*C.-C. HUANG<sup>1</sup>, P.-Y. WANG<sup>2</sup>;

<sup>1</sup>GIBMS, NTU, Taipei City, Taiwan; <sup>2</sup>Grad. Inst. of Brain and Mind Sci., Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan

**Abstract:** Dietary restriction (DR), particularly caloric restriction (CR)—defined as consuming 20% to 40% fewer daily calories while maintaining sufficient nutrition—has been shown to extend healthspan and enhance memory function through several interconnected biological pathways. DR promotes synaptic plasticity by upregulating plasticity-related genes such as brain-derived neurotrophic factor (BDNF) and stimulating adult hippocampal neurogenesis (AHN)—a process that generates new neurons and integrates them into existing circuits involved in memory function. Although the roles well-established roles of AHN in memory function, there has been no direct evidence linking DR-induced increment in AHN to improved memory performance. In our study, we directly tested whether AHN is essential for DR-induced memory enhancement

using two loss-of-function models: hippocampal X-ray irradiation and genetic ablation of AHN via T-box brain protein 2 (Tbr2) conditional knockout (cKO) mice. We first confirmed that DR robustly increases AHN, as evidenced by elevated numbers of proliferating cells (marked by Ki67) and immature neurons (marked by doublecortin, DCX), particularly in the dorsal hippocampus, a region specialized for spatial navigation and memory. However, in both the X-irradiated and Tbr2 cKO models, which lack proliferating progenitor cells and newborn neurons, DR failed to enhance memory performance. Consistent with the behavioral findings, the neurostructural changes typically induced by DR, including reduced dendritic arborization and increased spine density, were also attenuated when AHN was eliminated. These results suggest that AHN is a critical prerequisite for DR-induced memory improvements, providing direct evidence for the central role of hippocampal neurogenesis in mediating the cognitive benefits of dietary restriction. We believe this study would provide compelling evidence that AHN is essential for DR-induced memory enhancement. Further studies will focus on elucidating the underlying mechanisms by which DR enhances AHN and identifying potential druggable targets to replicate the cognitive benefits of DR.

**Disclosures:** C. Huang: None. P. Wang: None.

## **Poster**

### **PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.07/A7

**Topic:** A.01. Neurogenesis and Gliogenesis

**Title:** The Powerhouse of Neuronal Plasticity in Adulthood: Elucidating the Role of Mitochondrial Protein, CHCHD2, in Adult Neurogenesis and Hippocampal Function.

**Authors:** \*N. STEWART<sup>1</sup>, J. SONG<sup>2</sup>;

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**Abstract:** Adult hippocampal neurogenesis (AHN) is a dynamic yet understudied process whereby an endogenous pool of neural stem cells (NSCs) in the hippocampal dentate gyrus (DG) makes fate decisions to become adult-born neurons (ABNs). ABNs integrate into the existing circuitry to enhance DG-dependent functions such as memory consolidation and emotional processing during a two-week critical window. Recently, there has been an explosion of research into the role of mitochondria as central regulators of AHN, however few studies have explored how mitochondrial function directly influences NSC behaviors. I target a mitochondrial protein, Coiled-Coil-Helix Coiled-Coil-Helix Domain Containing 2 (CHCHD2) that canonically functions to upregulate mitochondrial complex IV activity and inhibit mitochondrial fusion to enhance oxidative phosphorylation. CHCHD2 is an ideal gene to study mitochondrial influence on AHN as CHCHD2 expression is high in NSCs and declines steadily along the neurogenic lineage. I leveraged the lox-Cre recombinase system to conditionally knockout (cKO) CHCHD2

in NSCs and label NSCs with a tdTomato reporter to perform lineage tracing at different time points following cKO of CHCHD2. Specifically, I quantified tdTomato positive cells colabeled with: Sox2 (expressed in early progenitors), Tbr2 (late-neuronal progenitors), DCX (immature neurons), and NeuN (mature neurons). Subsequently, I analyzed morphological changes to ABN dendritic complexity and spine density by Sholl analysis and 3-D reconstruction of ABN filaments respectively. Lastly, I assessed DG-dependent behaviors with novel place recognition for spatial memory and elevated zero maze for anxiety to assess how cKO of CHCHD2 impacts ABN integration into the DG circuitry. 7 days after cKO of CHCHD2, NSCs become highly proliferative and the NSC pool depletes. Additionally, NSCs exhibit precocious differentiation, leading to a transiently increased production of DCX<sup>+</sup> immature neurons that failed to survive one week later. Interestingly, the few immature neurons that survived into the critical window exhibit impaired dendritic morphology such as decreased dendritic intersections and reduced spine density. These cKO animals demonstrated significant impairments to spatial memory with no change in anxiety-like behaviors. These findings indicate that cKO of CHCHD2 induces NSCs to precociously mature into morphologically impaired neurons that fail to survive and properly integrate into the existing DG circuitry. These findings reveal CHCHD2 to be a critical regulator of NSC development into a neuronal fate and suggest CHCHD2 as a potential pharmacological target to augment AHN.

**Disclosures:** N. Stewart: None. J. Song: None.

## **Poster**

### **PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.08/A8

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** R01AA031028  
R01AA27766

**Title:** Cell type specific functions of Mef2c in regulating adult hippocampal neurogenesis and social behavior

**Authors:** \*S. BASU, E. RO, H. SUH;  
Neurosciences, Lerner Res. Institute, Cleveland Clin., Cleveland, OH

**Abstract:** Genetic and environmental factors have been found to play a crucial role in the development of autism spectrum disorder (ASD), but the precise mechanism underlying ASD has not been elucidated. Multiple animal models that harbor mutations in *Mef2c* have provided compelling evidence that *Mef2c* is indeed an ASD associated gene. However, studies in mice with germline or global brain knockout of *Mef2c* are limited in their ability to identify the precise neural substrates and cell types that are required for the expression of *Mef2c*-mediated ASD behaviors because it is expressed in multiple cell types that include neurons and microglia. To

determine the role of *Mef2c* in neurons in ASD, we first conditionally deleted *Mef2c* (*Mef2c*<sup>Neuronal cko</sup>) in hippocampal newborn neurons, which play a critical role in cognitive and social behaviors. This approach revealed that this specific deletion of *Mef2c* reduced the production, survival, structural development, and synaptic transmission of hippocampal newborn neurons. Moreover, the structural and functional impairments of hippocampal newborn neurons led to deficits in social interaction and social novelty recognition in *Mef2c*<sup>Neuronal cko</sup>, which are key characteristics of ASD behaviors. We next deleted *Mef2c* specifically in microglia (*Mef2c*<sup>microglial cko</sup>) and investigated its effects on hippocampal neurogenesis. The specific deletion of *Mef2c* in microglia also reduced hippocampal neurogenesis and interfered with structural development of hippocampal newborn neurons. Furthermore, social novel discrimination was disrupted in *Mef2c*<sup>microglial cko</sup> mice. Taken together, our study shows that *Mef2c* in both newborn neurons and microglia plays an essential role in hippocampal neurogenesis and ASD behavior. We are currently investigating the molecular and cellular mechanisms by which *Mef2c* regulates neurogenesis and social behaviors.

**Disclosures:** S. Basu: None. E. Ro: None. H. Suh: None.

## **Poster**

### **PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.09/A9

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** RS-2021-NR062028

**Title:** Exercise-induced systemic zinc mobilization enhances adult hippocampal neurogenesis and mitigates age-related cognitive decline

**Authors:** M. PARK<sup>1</sup>, S. SHIN<sup>1</sup>, S. SUH<sup>1</sup>, \*B. CHOI<sup>2,3</sup>;

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**Abstract:** Physical exercise enhances adult hippocampal neurogenesis (AHN) and cognitive function, yet the molecular mechanisms remain unclear. Neurogenesis occurs in the subgranular zone of the dentate gyrus (DG), where vesicular zinc is highly concentrated in presynaptic terminals. Zinc plays a critical role in synaptic plasticity, but its involvement in exercise-induced neurogenesis has not been fully elucidated. This study aimed to determine whether exercise-induced systemic zinc mobilization plays a role in promoting AHN and mitigating age-related cognitive decline. Wild-type and ZnT3 knockout mice underwent exercise training five times per week for 1 or 4 weeks. BrdU was intraperitoneally administered twice daily for 4 consecutive days, beginning 1 week after the adaptation period. One week post-running, histological analyses were performed to assess cell proliferation, neuroblast production, and ZnT3 expression in the

DG. Four weeks post-running, cognitive function was evaluated using the Barnes maze and Morris water maze, followed by histological assessments of the survival and phenotypes of newly generated cells. Our results demonstrate that ZnT3, a membrane zinc transporter responsible for concentrating  $\text{Zn}^{2+}$  into neuronal presynaptic vesicles, is not essential for the exercise-induced increase in AHN. Instead, exercise promoted systemic zinc mobilization, which may enhance neurogenesis through alternative zinc transport pathways. Treadmill running significantly increased hippocampal progenitor cell proliferation and adult neurogenesis, regardless of ZnT3 expression. Moreover, the combination of dietary zinc supplementation with exercise further enhanced neurogenesis and reversed age-related cognitive decline, suggesting a potential therapeutic strategy for aging-related cognitive dysfunction. These findings suggest that exercise-induced systemic zinc mobilization plays a key role in activating quiescent hippocampal progenitor cells and promoting their integration into the neurogenic pathway. This study provides new insights into the interplay between systemic zinc dynamics and neuroplasticity, highlighting the potential of exercise and zinc supplementation as a therapeutic approach for aging-related cognitive decline.

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## **Poster**

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**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR199.10/A10

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** NIH Grant NS086965  
NIH Grant NS085171

**Title:** Transcriptomic changes associated with aberrant activation of neural stem cells in a mouse model of Alzheimer's disease neuropathology

**Authors:** \*Y. FURUTA<sup>1</sup>, H. CHEN<sup>2,4</sup>, J. JIA<sup>2,4</sup>, T.-C. LU<sup>3</sup>, J. WANG<sup>1</sup>, Y. QI<sup>3</sup>, H. LI<sup>3</sup>, J. CHIN<sup>1</sup>;

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**Abstract:** Adult neurogenesis in the dentate gyrus (DG) contributes to cognitive function and mood regulation, and reduced neurogenesis is observed in chronic stages of temporal lobe epilepsy and Alzheimer's disease (AD). Utilizing transgenic mice that express mutant human amyloid precursor protein (APP mice) as a model of AD neuropathology, we previously showed that spontaneous epileptiform activity drives aberrant neural stem cell (NSC) activation and neurogenesis, followed by accelerated depletion of a finite pool of NSCs, resulting in chronic reductions in neurogenesis. However, the molecular mechanisms by which epileptiform activity

disrupts NSC and neurogenesis dynamics are unclear. A comprehensive understanding of epileptiform activity-dependent mechanisms may hold promise towards developing novel therapeutics to normalize neurogenesis in AD. To this end, we conducted single-nucleus RNA-sequencing of the DG to investigate cell-type-specific transcriptomic differences between young APP mice early in disease progression and nontransgenic (NTG) littermates. Differentially expressed gene (DEG) analysis found DEGs in both NSCs and neighboring cells that may be related to aberrant NSC activation. To further explore microenvironmental influences on NSC regulation, we performed differential cell-cell communication analysis in each cell type pair. This analysis revealed differential ligand-receptor interactions between mature granule cells (GCs) and NSCs or astrocytes and NSCs that may drive aberrant NSC activation. Pathway prediction analysis estimated intracellular signaling pathways activated by the differential ligand-receptor interactions in NSCs that could lead to NSC activation. Lastly, we analyzed the neurogenesis trajectory to assess whether the general process of neurogenesis is altered in APP mice. Although there is a difference in lineage progression after the neurogenic cells become mature GCs, APP and NTG mice exhibit a similar trajectory topology throughout neurogenesis. Together, our dataset reveals cell-type-specific transcriptomic changes early in disease progression in a mouse model of AD neuropathology and could be a valuable resource to understand the mechanisms initiating aberrant NSC dynamics in AD-related conditions.

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## **Poster**

### **PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.11/A11

**Topic:** A.01. Neurogenesis and Gliogenesis

**Title:** Maturation Neural Circuits Controlling Micturition Related Pelvic Viscero Motor Functions in Postnatal Rats

**Authors:** \*A. NITABARA, K. FUNAKOSHI;  
Yokohama City Univ., Yokohama, Japan

**Abstract:** Pelvic visceromotor functions, including micturition, are regulated by autonomic and somatic motor pathways from the central nervous system. These functions involve coordination between the parasympathetic system, which contracts the detrusor muscle, and the somatic system which controls the external urethral sphincter. The neural circuits responsible for micturition include Barrington's nucleus and spinal motoneurons in the intermediolateral nucleus (IML) and Onuf's nucleus. Corticotropin-releasing hormone (CRH) modulates these circuits. While traditionally linked to stress, CRH also influences neural plasticity, particularly in regions controlling visceral functions. Barrington's nucleus CRH-ergic projections, regulates motoneuron activity in the IML and probably the Onuf's nucleus. Perineuronal nets (PNNs) are

extracellular matrix structures surrounding neurons, stabilizing synapses and limiting plasticity. PNN formation follows a sex-dependent and temporally regulated patterns, affecting neural maturation. This study explores the relationship between CRH projections and PNN formation in spinal motoneurons in the IML and Onuf's nucleus. Immunohistochemical analysis using anti-ChAT, anti-CRF antibodies and WFA lectin was performed on Wistar rat spinal cords at postnatal days P1, P5, P10, P15, P20, P25, P35, and P60. CRH immunoreactivity was observed at P5 in both the IML and Onuf's nucleus, increasing progressively with age. By P60, CRH in Onuf's nucleus showed sexual dimorphism, with males exhibiting higher immunoreactivity than females. Similarly, PNN formation showed sex-specific patterns: males exhibited earlier PNN formation in the IML by P25, while females showed earlier formation in Onuf's nucleus. These findings suggest that PNN formation in pelvic motoneurons occurs later than in somatic motoneurons, indicating extended plasticity. This prolonged plasticity may offer a longer recovery window for pelvic functions after spinal cord injury compared to other motor systems. The sexual dimorphism in CRH immunoreactivity and PNN formation may reflect the influence of sex hormones, impacting recovery strategies. These results are critical for understanding pelvic function recovery and therapeutic approaches tailored to age and sex.

**Disclosures:** A. Nitabara: None. K. Funakoshi: None.

## **Poster**

### **PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.12/A12

**Topic:** A.01. Neurogenesis and Gliogenesis

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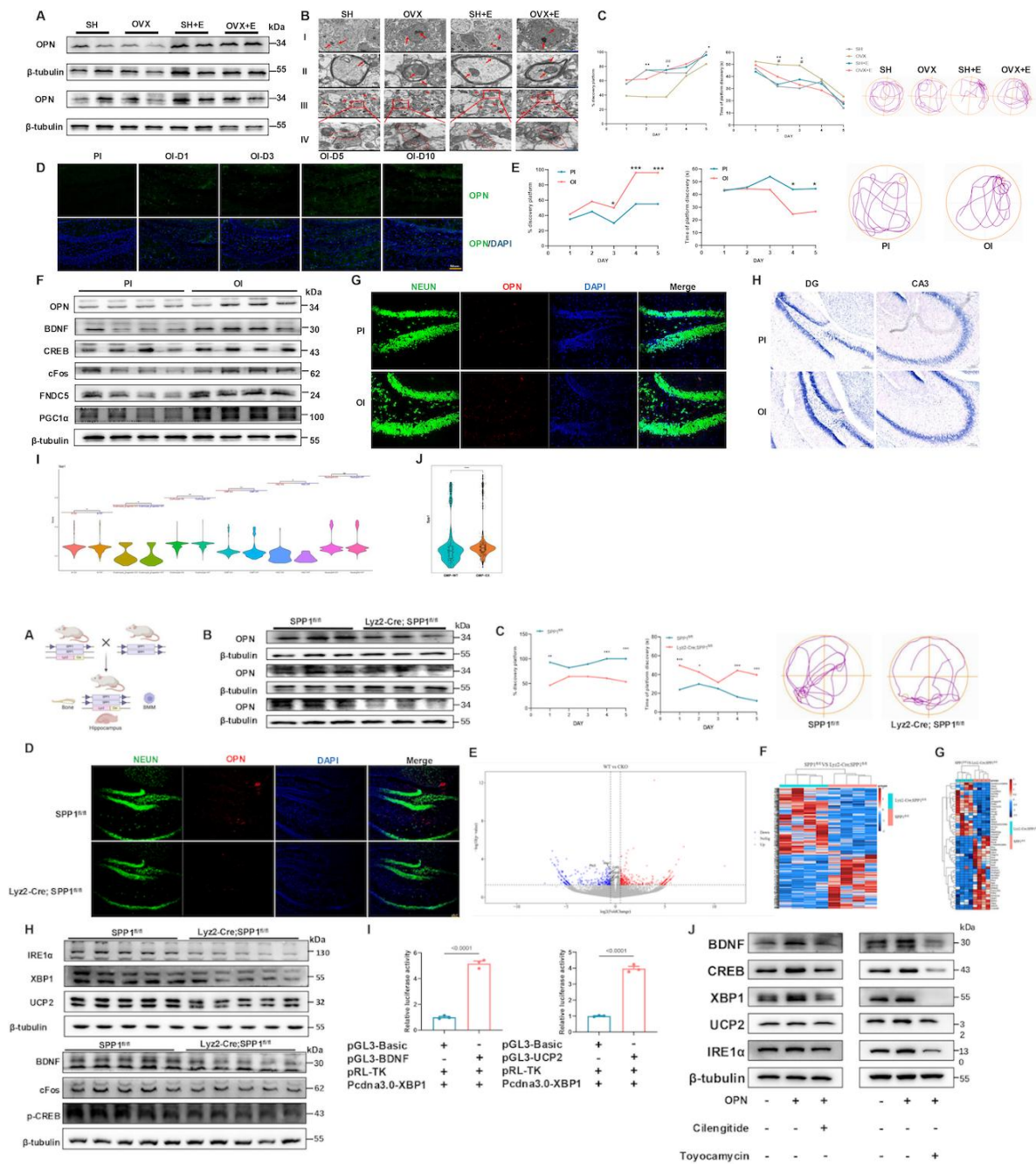
**Title:** Bone-derived osteopontin enhances cognitive function via XBP1/BDNF signaling

**Authors:** \*L. MAO<sup>1</sup>, L. WANG<sup>1</sup>, Q.-G. ZHANG<sup>2</sup>, K. M. DHANDAPANI<sup>1</sup>, J. ZOU<sup>3</sup>;  
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**Abstract:** Osteopontin (OPN), a glycosylated phosphoprotein secreted by bones, plays a vital role in infant growth and development. Since exercise has been shown to enhance OPN expression levels within bone tissue, we postulate that exercise facilitates the advancement of brain structure and function, potentially through its close association with bone-derived OPN. Our study found that aged and ovariectomized (OVX) mice exhibited compromised bone metabolism and cognitive function, along with reduced OPN levels in both bone and hippocampus. Intravenous administration of mouse OPN recombinant protein augmented the expression of hippocampal neurodevelopment-related factors and enhanced the cognitive abilities in developing mice. Single-cell sequencing revealed that exercise augmented the



expression of OPN in myeloid cells. The specific knockout of OPN (SPP1) in myeloid cells (lyz2-cre) impairs hippocampal structure and function. RNA sequencing and dual luciferase reporter assays confirmed that the OPN - XBP1 - BDNF/UCP2 pathway is crucial for regulating hippocampal structure and function in mice. Therefore, our study demonstrates that bone-derived OPN may play a crucial role in hippocampal development in the physiological state.



**Disclosures:** L. Mao: None. L. Wang: None. Q. Zhang: None. K.M. Dhandapani: None. J. Zou: None.

## Poster

### PSTR199: Postnatal Neurogenesis

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.13/A13

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** Lafayette Parish Medical Society Endowed Professorship  
UL Lafayette ADVANCE Minigrant, The Student Center for Research,  
Creativity and Scholarship

**Title:** Fibroblast Growth Factor Receptor 1 signaling in hypothalamic tanycyte development, interactions with diet and sex

**Authors:** \*C. HEALEY<sup>1</sup>, J. STAGRAY<sup>1</sup>, A. CHISTOSERDOV<sup>4</sup>, J. FISER<sup>2</sup>, K. M. SMITH<sup>3</sup>;  
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Louisiana, Lafayette, Lafayette, LA

**Abstract:** Fibroblast Growth Factor Receptor 1 (FGFR1) is a tyrosine kinase receptor expressed in glial cells of the hypothalamus, particularly in tanycytes of the ventricular zone. FGFR1 is known to induce cell proliferation and growth in multiple cellular contexts, and to influence gene expression and cellular responses through second messenger signaling such as mitogen activated protein kinase (MAPK), PI3K, and Phospholipase C  $\gamma$ /Calcium signaling cascades. Tanycytes are radial glial-like astrocytes with cell bodies present in the subventricular zone of the 3<sup>rd</sup> ventricle (3V) with long processes into the hypothalamic nuclei. In adult mice, tanycytes retain stem cell properties, and their daughter cells migrate and integrate into hypothalamic nuclei, such as the arcuate nucleus (ARC). There are two main types of tanycytes in the brain,  $\alpha$  tanycytes, which line the lateral walls of the third ventricle (3V), and  $\beta$  tanycytes, which reside ventrally along the median eminence. Tanycytes are implicated in glucose homeostasis and appetitive behaviors via response to glucose and endocrine ligands including Leptin, Ghrelin, and Fgf21. We previously demonstrated that inactivation of *Fgfr1* in glial stem cells resulted in reduced  $\beta$  tanycyte process length and impaired glucose tolerance after one month on a high fat diet. HFD also reduced SOX2 positive cell number along the 3V. Here, we examine sex differences in male and female *Fgfr1* conditional knockout mice (cKO) and control mice after a 60-day high fat diet (HFD), the length of time after which the HFD is expected to induce diabetes in control mice on a control diet. We found that female *Fgfr1* cKO mice had impaired glucose tolerance at day 0 and 30 days of a high-fat diet (HFD) compared to age-matched wildtype controls on the same diet. Animals in all groups gained weight from baseline. Significantly, the differences in glucose tolerance at 30 days occurred without differences in body weight change between genotypes. By 60 days of HFD, all groups had developed impaired glucose tolerance. Immunohistochemistry was performed to characterize the cell markers associated with neural stem and progenitor cells and adult neurogenesis in the hypothalamus and hippocampus (PCNA, GFAP, VIM).

Quantification of cell staining was assessed using ImageJ software. Our findings suggests that females lacking *Fgfr1* are more susceptible to diet-induced changes in glucose tolerance.

**Disclosures:** C. Healey: None. J. Stagray: None. A. Chistoserdov: None. J. Fiser: None. K.M. Smith: None.

## **Poster**

### **PSTR199: Postnatal Neurogenesis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR199.14/A14

**Topic:** A.01. Neurogenesis and Gliogenesis

**Support:** R01NS127973

**Title:** Formation of the inner ear and cochlear nuclei depends on *lmx1a/b* dosage in mouse development.

**Authors:** \*I. ISKUSNYKH<sup>1</sup>, S. CERVANTES ABRAHAM<sup>1</sup>, B. FRITZSCH<sup>2</sup>, V. V. CHIZHIKOV<sup>1</sup>;

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**Abstract:** The development of auditory and vestibular systems is regulated by transcription factors, which play an important role in cell specification, neurogenesis, and migration. Evolutionarily conserved transcription factors such as *Lmx1a* and *Lmx1b* are required for neurogenesis and inner ear development. Previously, we reported that the combined loss of *Lmx1a* and *Lmx1b* leads to an absence of the organ of Corti and disrupts the embryonic development of the spiral ganglion. However, whether the disruption of auditory and vestibular systems development continues postnatally and how it depends on dosages of *Lmx1a/Lmx1b* remains unknown. Our current study demonstrates that reduced auditory central projections and glutamatergic neuronal populations in embryonic ventral and dorsal cochlear nuclei are associated with decreased *Lmx1a/b* gene dosage. Most importantly, the loss of one copy of *Lmx1b* in embryos on *Lmx1a* <sup>-/-</sup> background results in a more severe phenotype as well as leads to a reduced number of *Atoh1*<sup>+</sup> progenitors in the lower rhombic lip (RL) compared to *Lmx1a*<sup>-/-</sup> mice, which may contribute to cochlear nucleus developmental defects. Normally, auditory central projections are supposed to reach the ventral cochlear nuclei, however, their absence is consistent with diminished *Lmx1b* expression. Notably, a substantial decrease in glutamatergic neuronal populations and their central projections persists postnatally in *Lmx1a/b* mutant mice, correlating with a reduced *Lmx1a/b* gene dosage. The spatial arrangement and length of central projection fibers also differ significantly. Similar to the embryonic stage, collateral fibers from the apex continue to overlap with basal fibers in postnatal *Lmx1a*<sup>-/-</sup>*Lmx1b*<sup>+/-</sup> mice. Taken together, our data indicate that the formation of the mammalian inner ear and its central

projections depend on Lmx1a/b gene dosage at both embryonic and postnatal developmental stages.

**Disclosures:** I. Iskusnykh: None. S. Cervantes Abraham: None. B. Fritzsche: None. V.V. Chizhikov: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.01/A15

**Topic:** A.06. Developmental Disorders

**Support:** NIMH 1F30MH135660  
NIGMS T32 GM008042  
NIGMS T32 GM152342

**Title:** Intrinsic activation in human stem cell-derived microglia harboring ASD risk gene *CHD8* haploinsufficiency mutations

**Authors:** \*N. M. HAWKEN, J. M. MARTIN, R. KAWAGUCHI, D. H. GESCHWIND;  
Neurol., UCLA, Los Angeles, CA

**Abstract:** Heterozygous loss of function mutations in chromodomain-helicase-DNA-binding-protein 8 (*CHD8*), a chromatin remodeling enzyme expressed most strongly during fetal cortical development, are a significant risk factor for Autism Spectrum Disorder (ASD). While ASD genetic risk resides primarily in developing neurons, post mortem cortical tissue from individuals with ASD reveals prominent activation of microglia. To this point, most autism research has centered around *CHD8*'s impact on neuronal function, despite expression of this gene in microglia. We aimed to investigate functional alterations in human stem cell-derived microglia with heterozygous loss of function mutations in *CHD8*. Control human stem cell (SC) lines, one male iPSC line KOLF2.2J and one female embryonic SC line HUES66, were previously CRISPR edited for heterozygous mutations in *CHD8*, producing two clones per line. SC were differentiated into mature microglia (diffMG) with growth factors ( $n \geq 5$  per clone). Bulk RNA sequencing was performed on diffMG to assess differential gene expression, gene networks, and correlation to *in vivo* microglial signatures. Phagocytic capacity and migration were characterized through live cell time-lapse imaging of diffMG exposed to synaptosomes labeled with pH-sensitive dye pHrodo Red SE. *CHD8* mutant diffMG have significant differential gene expression relative to control cells (2283 genes up & 1728 down,  $\log_{2}FC > 0.2$ ,  $FDR < 0.05$ ). Upregulated GO pathways, as determined by GSEA, mostly relate to activated microglial phenotypes, but some pathways relate to the known molecular function of *CHD8* as a chromatin modifier. *CHD8* mutant diffMG gene expression best matches the reactive microglia that are increased in post mortem cortex from patients with ASD (FGSEA NES = 2.32, adj p-val =  $2.2e-11$ ), and gene sets parallel to those that are upregulated in reactive microglia in ASD are

upregulated in these mutant microglia (NES 2.04, adjusted p-val = 5.9e-20). Synaptosome uptake was also elevated in the *CHD8* mutant microglia, as measured by pH dye signal relative to cell area over time, consistent with a functional impact. *CHD8* haploinsufficiency alters human stem cell-derived microglia gene expression and phagocytosis, in a manner similar to post-mortem cortical microglia in ASD. This work is the first step in interrogating how microglia respond to cell-intrinsic genetic risk versus secondary effects based on primary neuronal dysfunction. Our next steps are to interrogate whether non-mutant microglia show similar changes when cultured with *CHD8* mutant neurons.

**Disclosures:** N.M. Hawken: None. J.M. Martin: None. R. Kawaguchi: None. D.H. Geschwind: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.02/A16

**Topic:** A.06. Developmental Disorders

**Title:** A crosstalk between nitric oxide and mTOR signaling pathway in autism spectrum disorder

**Authors:** \*S. OJHA<sup>1</sup>, M. KARTAWY<sup>2</sup>, M. K. TRIPATHI<sup>4</sup>, W. HAMOUDI<sup>5</sup>, H. AMAL<sup>3</sup>;  
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<sup>4</sup>Sch. of Pharm., Hebrew Univ., Jerusalem, Israel; <sup>5</sup>Sch. of Pharm., The Hebrew Univ. of Jerusalem, Jerusalem, Israel

**Abstract:** Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by complicated genetic and molecular mechanisms. We previously showed that nitric oxide (NO) plays a role in ASD. However, the precise molecular mechanism that NO plays via its posttranslational modification, S-nitrosylation (SNO), in ASD remains largely unknown. Emerging evidence, including our previous studies, suggests that the mechanistic target of the rapamycin (mTOR) signaling pathway plays a critical role in ASD pathophysiology. Our systems biology of the SNO-proteome showed the significance enrichment of mTOR pathway. In this study, we deciphered the impact of S-nitrosylation on the mTOR pathway in the pathology using mouse models as well as clinical samples of kids with ASD. To assess changes in the SNO-proteome, we used the SNO-trap method, revealing increased S-nitrosylation of tuberous sclerosis complex 2 (TSC2) in *Shank3*<sup>Δ4-22</sup> and *Cntnap2*<sup>(-/-)</sup> mutant mice. We proved that this modification led to the loss of TSC2 function via autoubiquitination, resulting in dysregulated mTOR signaling. Pharmacological inhibition of neuronal nitric oxide synthase (nNOS) successfully prevented TSC2 S-nitrosylation, mTOR overactivation, and altered protein translation in ASD models, highlighting NO's role in modulating mTOR function. Furthermore, the administration of TG003, an mTOR activator, in wild-type (WT) mice induced ASD-like behaviors, proving the direct link between mTOR hyperactivation and autistic phenotypes. To

further validate the role of TSC2 S-nitrosylation in ASD, we generated a cysteine-to-serine mutation (C203S) in TSC2 to prevent its S-nitrosylation. Intracranial injection of the mutant TSC2(C203S) in *Shank3*<sup>Δ4-22</sup> knockout (KO) in prefrontal cortex prevented ASD-like behaviors, confirming the pathogenic role of NO-mediated TSC2 modification. Importantly, analysis of clinical ASD samples revealed decreased TSC2 levels and increased mTOR signaling activity, further supporting our findings. Collectively, this study uncovers a novel molecular mechanism by which S-nitrosylation disrupts TSC2 function, leading to aberrant mTOR signaling and ASD-like phenotypes.

**Disclosures:** S. Ojha: None. M. Kartawy: None. M.K. Tripathi: None. W. Hamoudi: None. H. Amal: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.03/A17

**Topic:** A.06. Developmental Disorders

**Support:** ANR EMTSENS

**Title:** Disrupted Mechanosensory Processing in Autism: The Contribution of Spinal GABAergic Interneurons

**Authors:** \*A. SAINT-JEAN<sup>1</sup>, V. ROUGLAN<sup>1</sup>, F. SPECQUE<sup>2</sup>, A. GROUPI<sup>2</sup>, M. NIKOLSKI<sup>2</sup>, O. SEMELIDOU<sup>1</sup>, I. MATIAS<sup>1</sup>, A. FRICK<sup>1</sup>, A. FAVEREAUX<sup>3</sup>, Y. LE FEUVRE<sup>1</sup>;

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**Abstract:** Autism is characterized by impairments in social communication and interactions, as well as restricted behaviours. Most people with autism also exhibit aberrant reactivity to sensory stimuli including tactile stimuli. In addition to being a major source of discomfort for autistic people, recent research suggests that tactile dysfunction may actually contribute to the development of other autism core symptoms. This is why understanding the neural mechanisms behind tactile dysfunction is so important. Tactile information is perceived in the periphery and processed in the spinal cord under the control of inhibitory interneurons before being sent to higher brain structures. However, whether these inhibitory neurons undergo functional alterations in autistic models remains poorly understood.

To explore the functional plasticity of spinal GABAergic interneurons (SGI) in autism, we used *Fmr1*<sup>-y</sup> mice crossed with *Gad1*-GFP reporter lines. These mice exhibit haploinsufficiency for the *Gad1* gene, which may interfere with the development of characteristic autistic phenotypes. We show that *Fmr1*<sup>-y</sup>-*Gad1*-GFP mice display tactile deficits (longer latencies in tape removal test, decreased reactivity to brush stimulation), decreased anxiety in elevated plus maze, and lower social scores in the nest building test, as typically observed in autistic models.

We then characterize electrophysiologic, transcriptomic and morphologic properties of SGI in acute spinal slices using the patch-seq technique. We observed that SGI exhibit altered excitability, characterized by an increased firing frequency of action potentials (AP) at low current injections, but a reduced frequency at high intensities compared to WT mice. This results in a narrower functional dynamic range, shifted toward lower-intensity stimulations. Our findings suggest that this alteration stems from changes in ionic currents, specifically HCN currents contributing to increased sag ratios in *Fmr1*<sup>-/-</sup> mice and BKCa channels influencing the enhanced medium after-hyperpolarization. Importantly, transcriptomic analysis of recorded neurons reveals that these changes are restricted to a subpopulation of SGI expressing the parvalbumin (Pvalb) marker, consistent with the gatekeeper role attributed to spinal pvalb neurons in somatosensory processing.

Altogether, we suggest that functional alterations of SGI, particularly Pvalb neurons in autism models disrupt tactile information processing upstream of the brain and may play a critical role in the development of sensory and social deficits characteristic of autism, underscoring their potential as therapeutic targets.

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## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.04/A18

**Topic:** A.06. Developmental Disorders

**Support:** Pilot project NIH P30ES030283  
DOD Grant AR230178P1

**Title:** Reduced TREM2 and disruption of glutamate homeostasis in the cerebellum of a mouse model of Autism

**Authors:** \*R. JAGADAPILLAI<sup>1</sup>, E. GOZAL<sup>3</sup>, A. IKRAM<sup>4</sup>, N. NAGARAJAN<sup>4</sup>, G. N. BARNES<sup>2</sup>;

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**Abstract:** The triggering receptor expressed on myeloid cells 2 (TREM2), a receptor specifically expressed in microglia in the brain, promotes microglial proliferation and survival, regulates phagocytic activity and controls synaptic pruning during development. Additionally, TREM2 controls microglial metabolic pathways and the switch from M1 to M2 pro- / anti-inflammatory microglia, therefore regulating neuroinflammation. Human studies have shown decreased

TREM2 levels correlating with the severity of ASD symptoms. TREM2 <sup>-/-</sup> mice display increased neuroinflammation, enhanced excitatory transmission and have been shown to exhibit ASD-associated behavior. Previous studies in murine models of ASD have shown increased microglia activation, neuroinflammation and excitatory/inhibitory imbalance, and impaired social interactions, improved by TREM2 overexpression or by administration of soluble TREM2. However, the precise underlying mechanisms of TREM2 activity in ASD microglia have not been elucidated. Our present study attempts to establish whether changes in TREM2 expression in the cerebellum of BTBR mice, an established mouse model of ASD, may significantly correlate with decreased glutamate transport, affecting its clearance from the synaptic cleft, underlying the excitatory/inhibitory imbalance in ASD. We investigated whether TREM2, AQP4, and the glutamate transporters EAAT1, EAAT2, and vGLUT1 expression and co-localizations are altered in a BTBR mouse ASD model, using immunofluorescent staining and western blotting analysis. Our data show that TREM2, AQP4, EAAT1, EAAT2 and vGLUT1 expression significantly decreased in the BTBR cerebellum, compared to C57 mice. These findings suggest that TREM2 decrease in ASD may alter glutamate transport, resulting in increased excitotoxicity. In addition, we show reduced co-localization and expression of TREM2 with vGLUT1 in BTBR when compared to C57 mice, suggesting decreased vesicular glutamate uptake and sequestration of glutamate from intracellular stores, in presynaptic vehicles. Abnormal TREM2 signaling in BTBR mouse cerebellum, affecting synaptic pruning and immune response may underlie developmental defects in ASD subjects. Further understanding the role of TREM2 and its effect on ASD behavior may allow the development of novel targeted therapeutics alleviating ASD patients' symptoms.

**Disclosures:** R. Jagadapillai: None. E. Gozal: None. A. Ikram: None. N. Nagarajan: None. G.N. Barnes: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.05/A19

**Topic:** A.06. Developmental Disorders

**Support:** Division of Biology  
Project ACCESS  
PRIME

**Title:** Deciphering autism spectrum disorder neuropathology: exploring mTORC2 dysfunction in Rab-mediated Neurexin-1 transport

**Authors:** \*E. SWENSEN<sup>1</sup>, M. HUTTON<sup>2</sup>, D. L. HYND<sup>3</sup>;  
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**Abstract:** Autism spectrum disorder (ASD) is characterized by disrupted neuronal communication, particularly in the regulation of presynaptic proteins such as Neurexin-1 (NRX1), which are essential for synapse formation and function. Previous studies from our lab have shown that Rab GTPases (Rab3A, Rab27A, Rab37) seem to be important in regulating NRX1 vesicular transport. Dysregulation of the mammalian target of rapamycin (mTOR) pathway has been implicated in ASD, with both mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) being linked to alterations in neurodevelopment. mTORC2, which governs cytoskeletal dynamics, has been implicated in ASD neuropathology, but its role in Rab-mediated NRX1 trafficking remains unclear. Additionally, epigenetic alterations, such as DNA methylation in the dorsal raphe nuclei of individuals with ASD, affect genes involved in vesicle trafficking, including Rab-regulatory elements. This suggests a transcriptional dysregulation of Rab pathways in ASD pathophysiology. However, the mechanistic relationship between mTORC2 dysfunction and Rab-mediated NRX1 trafficking has not been fully explored. We hypothesize that mTORC2 dysfunction impairs Rab-mediated NRX1 transport, leading to synaptic mislocalization observed in ASD. To test this, we first characterized the localization and expression of mTORC2 in rat B35 neuroblastoma cells under serum and serum-free conditions. Confocal microscopy analysis revealed condition-dependent colocalization of the downstream mTORC2 marker, PKA/AKT, with Rab GTPases and NRX1. The strongest colocalization was observed under differentiating conditions, particularly with Rab3A and Rab37, suggesting mTORC2's potential involvement in regulating NRX1 vesicular transport. Further analysis using Western blotting and qPCR supported this potential mechanistic link between mTORC2 signaling and Rab-mediated NRX1 trafficking. Extending these findings, we are continuing this work in a more physiologically relevant model—rat cortical neurons. This will allow for a better understanding of how mTORC2 and Rab GTPases interact in a more complex, native environment, and how these pathways might be disrupted in ASD. These findings could ultimately link mTORC2 dysfunction as a contributor to synaptic mislocalization in ASD.

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## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.06/A20

**Topic:** A.06. Developmental Disorders

**Support:** Adelson Medical Research Foundation  
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NIH Grant P50HD103557

**Title:** Pten and mtor pathway regulation of human neurite outgrowth

**Authors:** \*M. C. CONDRIO<sup>1</sup>, K. TESSEMA<sup>2</sup>, L. ELAHI<sup>1</sup>, S. IRVIN<sup>1</sup>, R. KAWAGUCHI<sup>1</sup>, J. E. LE BELLE<sup>3</sup>, D. SAREEN<sup>4</sup>, R. SAMARASINGHE<sup>5</sup>, J. MARTINEZ<sup>1</sup>, M. F. WELLS<sup>6</sup>, R.

DAMOISEAUX<sup>1</sup>, H. I. KORNBLUM<sup>7</sup>;

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**Abstract:** A challenge in understanding and treating Autism Spectrum Disorder (ASD) is the diversity of underlying genetic and functional mechanisms involved. While no single gene or pathway is responsible for all cases, the PI3K-AKT-mTOR pathway is one that has been linked to ASD, macrocephaly, abnormal neuronal connectivity, and behavior. PTEN is a negative regulator of PI3K activity, and therefore activates mTOR downstream. PTEN mutations have been associated with ASD and macrocephaly, though the mechanism(s) by which this occurs has not yet been determined. Inhibition or deletion of PTEN in rodent and human models have been shown to increase neurite outgrowth. Here, we investigate the impact of PTEN mutations on neurite outgrowth and neuronal activity in NGN2-induced neurons differentiated from iPSCs originating from patients that were both diagnosed with ASD and macrocephaly. We compared the effects of the endogenous mutation with isogenic lines in which either the PTEN mutation was corrected to wild type via CRISPR editing or PTEN was fully knocked out. We measured neurite outgrowth by automated image acquisition and analysis and compared neurite outgrowth in cells with both PTEN deletion and mutations. Loss of PTEN resulted in an increase in neurite outgrowth, though the effects of patient mutations are variable, depending on the mutation. The effect of increased neurite outgrowth was not completely abrogated by treatment with rapamycin, indicating that PTEN may inhibit neurite outgrowth through mechanisms other than the mTOR pathway. Our results thus far suggest that the extent to which patient-associated PTEN mutations contribute to altered neuronal development and connectivity is variable and may depend on the level of PTEN function, which could be modulated by environmental factors. Current studies are examining the role of patient-derived PTEN mutations in more complex model systems.

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## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.07/A21

**Topic:** A.06. Developmental Disorders

**Support:** NIMH Grant 5R01MH132921  
Jerome Lejeune Foundation  
Colorado State University

**Title:** The role of prefrontal delta-catenin in social behavior

**Authors:** \*A. LOPEZ SANMIGUEL<sup>1</sup>, R. ROACH<sup>2</sup>, S. ROH<sup>3</sup>, H. MENDEZ-VAZQUEZ<sup>4</sup>, R. LEE<sup>4</sup>, H. KIM<sup>3</sup>, S. KIM<sup>4</sup>;

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**Abstract:** The glycine 34 to serine (G34S) mutation in the  $\delta$ -catenin gene has been found in autism spectrum disorder (ASD) patients and results in loss of  $\delta$ -catenin functions at excitatory synapses, which is presumed to underlie ASD pathogenesis in humans. However, how the G34S mutation causes loss of  $\delta$ -catenin functions to induce ASD remains unclear. In this study, we found that synaptic  $\delta$ -catenin and GluA2 levels in the cortex were significantly decreased in mice harboring the  $\delta$ -catenin G34S mutation. The G34S mutation increased glutamatergic activity in cortical excitatory neurons while it was decreased in inhibitory interneurons, indicating changes in cellular excitation and inhibition.  $\delta$ -catenin G34S mutant mice also exhibited social dysfunction, a common feature of ASD. Similar changes were also found in parvalbumin-positive (PV+) inhibitory interneurons and excitatory cells in the KO medial prefrontal cortex (mPFC). Most importantly, pharmacological inhibition of GSK3 $\beta$  activity reversed the G34S-induced loss of  $\delta$ -catenin function effects in cells and mice. Additionally, using  $\delta$ -catenin knockout (KO) mice, we confirmed that  $\delta$ -catenin as required for GSK3 $\beta$  inhibition-induced restoration of normal social behavior in  $\delta$ -catenin G34S mutant animals. Finally, we demonstrated altered prefrontal network activity that is associated with social interaction in G34S mice. Taken together, we reveal that the loss of  $\delta$ -catenin functions arising from the ASD-associated G34S mutation induces social dysfunction via alterations in the activity at synaptic, cellular, and network levels and that GSK3 $\beta$  inhibition can reverse  $\delta$ -catenin G34S-induced synaptic and behavioral deficits

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**Poster**

**PSTR200: Autism: Synaptic and Cellular Mechanisms**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.08/A22

**Topic:** A.06. Developmental Disorders

**Support:** FAPESP Project No.: 2024/14288-0  
CNPQ Project No.: 153574/2024-0  
CNPQ Project No.: 406258/2022-8

**Title:** Unraveling STIP1 function in maternal autoantibody-related autism: from molecular mechanisms to human brain organoid models

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**Abstract:** Autism spectrum disorder (ASD) encompasses a range of neurodevelopmental conditions with complex phenotypes and multifactorial etiology, including genetic, epigenetic, metabolic, immunological, and environmental factors. A distinct subtype, maternal autoantibody-related ASD (MAR-ASD), involves maternal autoantibodies (MAR<sup>Abs</sup>) that cross the placental and blood-brain barriers during gestation and target fetal brain proteins, contributing to more severe ASD phenotypes. Despite its clinical relevance, MAR-ASD remains understudied, particularly in genetically diverse populations, such as Brazil. One MAR<sup>Ab</sup> target, the stress-inducible phosphoprotein 1 (STIP1), is a co-chaperone of HSP70/HSP90 with key roles in proteostasis, neuronal differentiation, neuritogenesis, and synaptic plasticity. STIP1 knockout in mice leads to embryonic lethality and degeneration of the neural tube. Previous work from our group showed that STIP1 supports stemness and pluripotency in mouse embryonic stem cell models. However, despite being a target of MAR<sup>Abs</sup>, the contribution of STIP1 to neurodevelopment and neurodevelopmental processes relevant to MAR-ASD remains unclear. To address that, our work aims to investigate the implications of STIP1 in neurodevelopment and the molecular mechanisms involved in MAR-ASD. Using public transcriptomic data from human brains, we found that STIP1 expression correlates with several genes expressed in radial glial cell zones, progenitors previously implicated in MAR-ASD. While genes positively correlated with STIP1 are involved in neural tube formation and closure, negatively correlated genes include those regulating proteostasis and neuronal maturation. Proteomic profiling of STIP1-knockdown human iPSCs (hiPSCs) revealed overlap with protein expression signatures present during neural differentiation, including altered chaperones and co-chaperones, cytoskeletal regulators, and proteins involved in synaptic signaling and apoptosis. In vitro, preliminary assays showed increased STIP1 expression upon hiPSC neuronal differentiation and maturation. Finally, we established cerebral organoid cultures to enable functional studies of STIP1 modulation and autoantibody exposure in a human 3D neurodevelopmental model relevant to MAR-ASD, such as neural tube and brain organoid models. As a future perspective, we aim to establish the first Brazilian MAR-ASD cohort, uncovering the incidence and particularities of this subtype in Brazil and exploring the contribution of STIP1 to MAR-ASD pathophysiology, advancing our understanding of ASD in a broad and genetically diverse population.

**Disclosures:** C.F.L. Fernandes: None. M. Passos-Bueno: None. M.H. Lopes: None.

**Poster**

**PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.09/A23

**Topic:** A.06. Developmental Disorders

**Support:** RRF-2.3.1-21-2022-00011

**Title:** Neuronal activity impairments in iPSC-derived neurons from idiopathic autism neurons

**Authors:** \*A. KERN<sup>1</sup>, Z. NÉMETHY<sup>2</sup>, B. LENDVAI<sup>3</sup>;

<sup>1</sup>Gedeon Richter Plc, Budapest, Hungary; <sup>2</sup>Gedeon Richter Plc., Budapest, Hungary; <sup>3</sup>Richter Gedeon Plc, Budapest, Hungary

**Abstract:** Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder of the central nervous system involving persistent challenges with social communications, restricted interest and repetitive behavior. It is important to understand the underlying neuronal molecular mechanism to develop effective interventions to ASD. However, currently it is difficult to examine the ASD pathology and to develop treatments for these individuals. To study the molecular basis of ASD we utilized induced pluripotent stem cells terminally differentiated into neurons (iPSC-N) from idiopathic ASD and healthy control individuals (CTRL). These iPSC-N bearing a genetic background of patients and manifest the disease-specific pathophysiology and phenotypes. In our in vitro model system, we found significant decrease in spontaneous activity of ASD-iPSC-N compared to CTRL, suggesting the synaptic dysfunction in autistic neurons. Utilizing chemogenetic approach we confirmed that in ASD-iPSC-N neuronal network showed impaired synaptic neurotransmission and connectivity (measured by decreased  $[Ca^{2+}]_i$  waves and glutamatergic transmission). Furthermore, we found impaired actin dynamics in ASD-iPSC-N by monitoring real-time actin dynamics in spines. These data heavily support the idea that the impaired neuronal activity and synaptic dysfunction is a prominent feature of the human ASD.

**Disclosures:** A. Kern: A. Employment/Salary (full or part-time): Gedeon Richter Plc. Z. Némethy: A. Employment/Salary (full or part-time): Gedeon Richter Plc. B. Lendvai: A. Employment/Salary (full or part-time): Gedeon Richter Plc.

## **Poster**

**PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.10/A24

**Topic:** A.06. Developmental Disorders

**Support:** NJGCA Grant CAUT25GFP006  
NIH grant NS089578  
DOD grant W81XQH-18-1-0338

**Title:** Mark2 loss-of-function is associated with neuronal hyperexcitability and microglial dysregulation

**Authors:** \*H. CAIOLA<sup>1</sup>, E. M. DAPRANO<sup>3</sup>, Q. WU<sup>2</sup>, B. DANIELS<sup>3</sup>, K. MONAHAN<sup>3</sup>, Z. P. PANG<sup>4</sup>, H. ZHANG<sup>2</sup>;

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**Abstract:** Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is behaviorally defined by social and communication deficits and repetitive behaviors. In addition, a large proportion of ASD patients suffer from co-occurring conditions such as cognitive impairment and epilepsy, which suggests that these disorders exhibit pathological commonalities at the cellular and molecular levels. For instance, both ASD and epilepsy are associated with synaptic dysfunction and neuronal hyperexcitability. Therefore, understanding mechanisms in the brain that are vital for maintaining proper levels of neuronal excitability may help develop effective treatments for ASD patients suffering from co-occurring conditions. Microtubule affinity regulating kinase 2 (MARK2), also known as partitioning-defective 1b (Par1b), has recently been shown as an autism risk gene. ASD-associated mutations in MARK2 are primarily *de novo* and result in loss-of-function. Furthermore, ASD patients harboring *de novo* loss-of-function mutations in MARK2 exhibit co-occurring neurological conditions including cognitive impairment and epilepsy. This is consistent with *de novo* loss-of-function mutations in MARK2 found in neurodevelopmental disorders with epilepsy. Interestingly, we found that MARK2 knockout (MARK2<sup>-/-</sup>) mice exhibit ASD-like phenotypes including learning and memory deficits, reduced sociability, and synaptic dysfunction. Moreover, heterozygous deletion of MARK2 is sufficient to increase seizure susceptibility. Consistent with this observation, electrophysiological analysis of hippocampal slices indicates underlying neuronal hyperexcitability in MARK2 deficient neurons. Thus, MARK2 loss-of-function may contribute to ASD and epilepsy by producing an abnormal increase in neuronal excitability. Nonetheless, the mechanism by which MARK2 regulates neuronal excitability is completely unknown. Bulk RNAseq of MARK2<sup>-/-</sup> mice suggests dysregulation in genes regulating synaptic transmission and ion homeostasis. Remarkably, post-hoc deconvolution of the bulk RNAseq dataset revealed that microglia are likely contributors of the observed transcriptional dysregulation. This is in line with our previous report demonstrating that heterozygotic deletion of MARK2 in mice is sufficient to prime microglia leading to increased sensitivity to insults. Therefore, current efforts aim to determine microglial-mediated regulatory pathways that contribute to the neuronal hyperexcitability associated with loss of MARK2.

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## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.11/A25

**Topic:** A.06. Developmental Disorders

**Title:** The Gsk3 $\beta$ -mediated GABAergic and Glutamatergic alterations in the Cntnap2 mouse model of autism

**Authors:** \*M. KARTAWY<sup>1</sup>, S. OJHA<sup>1</sup>, M. K. TRIPATHI<sup>3</sup>, H. AMAL<sup>2</sup>;  
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**Abstract:** Core behaviors of autism spectrum disorder (ASD) have been reported in humans with CNTNAP2 mutation. This gene encodes a neuronal transmembrane protein member of the neurexin superfamily, which is essential for synaptic transmission and neural connectivity. The Cntnap2 knockout mice (Cntnap2<sup>-/-</sup>) exhibit essential ASD-like behavioral phenotypes. This study aims to elucidate the molecular mechanisms underlying the synaptic and behavioral deficits observed in Cntnap2<sup>-/-</sup> mice. We hypothesize that a mutation in the Cntnap2 gene leads to the reprogramming of protein expression and kinase signaling, potentially resulting in synaptic and behavioral dysfunction. Using the phosphoproteome platform, we found a significant reduction in phosphorylation levels of Gsk3 $\beta$  at serine 9 in the cortex of Cntnap2<sup>-/-</sup> mice. This site correlates with inhibition of its kinase activity. Gsk3 $\beta$  is a serine/threonine kinase that plays a key role in synaptic function and plasticity and acts as the main negative regulator of the WNT/ $\beta$ -catenin signaling pathway. We suggest that aberrant overactivation of Gsk3 $\beta$  in the cortex of Cntnap2<sup>-/-</sup> mice may contribute to synaptic and behavioral deficits. Based on our preliminary findings, Gsk3 $\beta$  phosphorylated  $\beta$ -catenin at serine 33, 37, and threonine 41, resulting in its ubiquitination and degradation in the brains of Cntnap2<sup>-/-</sup> mice. Treatment with a selective inhibitor of Gsk3 $\beta$  improved certain ASD-like behaviors, including sociability deficits and anxiety. These effects were accompanied by increased dendritic spine densities in the cortex. To decipher molecular underpinnings of these effects, we explored the role of Gsk3 $\beta$  at both inhibitory and excitatory synapses. Gsk3 $\beta$  phosphorylates the inhibitory scaffold protein gephyrin, triggering its cleavage. This may disrupt anchoring of GABAA receptor subunits to the synaptic plasma membrane, potentially reducing inhibitory inputs in the cortex, as measured by patch-clamp recordings. At excitatory synapses, Gsk3 $\beta$  regulates phosphorylation of the GluA1 AMPAR subunit, directing it toward lysosomal degradation, reducing excitatory synaptic input. Our in vitro findings suggest that increased Gsk3 $\beta$  activity in Cntnap2<sup>-/-</sup> mice is specific to excitatory and inhibitory neurons and does not extend to glial cells. Intracranial injection of AAV9 expressing constitutively active GSK3 $\beta$  induced anxiety and social deficits in C57BL/6 mice. This study uncovers novel molecular mechanisms at excitatory and inhibitory synapses in the Cntnap2 mouse model of ASD. These findings suggest that GSK3 $\beta$  may offer a promising therapeutic target for ASD-like behaviors associated with CNTNAP2 mutation

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## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.12/A26

**Topic:** A.06. Developmental Disorders

**Support:** Strategic Partnership Award for Research Collaboration  
Lo Kwee-Seong Biomedical Research Fund (J.I.)  
Faculty Innovation Award (FIA2020/A/04) from the Faculty of Medicine,  
CUHK (J.I.)  
Gerald Choa Neuroscience Institute Research Program Fund (J.I.)

**Title:** Genomic and Functional Investigation of the Role of *CACNB1* in Autism

**Authors:** \*M. CHAN<sup>1</sup>, J. IP<sup>2</sup>;

<sup>1</sup>The Chinese Univ. of Hong Kong, Sha Tin, Hong Kong; <sup>2</sup>Sch. of Biomed. Sci., The Chinese Uni of Hong Kong, Hong Kong, China

**Abstract:** Genomic and Functional Investigation of the Role of *CACNB1* in Autism **Authors:** Maggie See Wing, CHAN<sup>1</sup>, Ryan K.C. YUEN<sup>3,4</sup>, Jacque Pak Kan IP<sup>1,2</sup> <sup>1</sup>*School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong, China* <sup>2</sup>*Gerald Choa Neuroscience Institute, The Chinese University of Hong Kong, Hong Kong, China* <sup>3</sup>*The Hospital for Sick Children, The Hospital for Sick Children, Toronto, Ontario, Canada* <sup>4</sup>*Molecular Genetics, Medicine, University of Toronto, Toronto, Ontario, Canada*

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**Objective:** Autism spectrum disorder (ASD) is a complex neurological and developmental condition characterized by impairments in social interaction, repetitive behavior, and communication, with a multifactorial genetic origin. Although ASD can be diagnosed as early as 18 months of age based on developmental history and behavioral observation, the limited understanding of its genetic and molecular mechanisms hampers the development of effective therapies, highlighting the urgent need for therapeutic advancements. This study aims to investigate the genomic and functional aspects of an ASD risk gene, focusing specifically on novel repeat expansions in a calcium voltage-gated channel auxiliary subunit beta 1 (*CACNB1*) gene. Tandem repeat expansions in a novel risk locus, *CACNB1*, have been identified in individuals with ASD; however, less is known about its association with ASD. **Methods:** To elucidate the role of *CACNB1* in ASD, we employed a *Cacnb1* knockdown approach in rodent models, targeting ASD-relevant brain regions, such as the medial prefrontal cortex (mPFC). Behavioral assessments, including the three-chamber test, open-field test, and self-grooming analysis, were conducted to evaluate the severity of social impairments and repetitive behaviors.

**Results:** Results indicated that mice with *Cacnb1* knockdown in the mPFC exhibited heightened anxiety and reduced preference for social novelty. Furthermore, we investigated spine morphology in primary neurons to examine the relationship between morphological alterations and synaptic transmission. Our findings revealed that primary neurons with *Cacnb1* knockdown displayed less mature spine morphology, suggesting that *CACNB1* plays a critical role in the formation of mature dendritic spines. **Conclusion:** This project aims to elucidate the complex genetics of ASD by investigating the impact of novel genetic variants on *CACNB1* gene. Future work will focus on the molecular mechanisms underlying repeat expansion in *CACNB1* gene and its potential contributions to the manifestation of ASD symptoms.

**Keywords:** Medial prefrontal cortex, calcium voltage-gated channel auxiliary subunit

**Disclosures:** M. Chan: None. J. Ip: None.

**Poster**



## **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR200.13/A27

**Topic:** A.06. Developmental Disorders

**Support:** NIH 5R01MH097236-10  
NIH 5R21MH129806-02

**Title:** Multi-omic analyses reveal neuroimmune dysregulation in the amygdala of autistic individuals

**Authors:** \*E. C. HALEY<sup>1,3</sup>, E. L. CARLSON<sup>1,3</sup>, J. VAN DE WATER<sup>2,3</sup>, C. M. SCHUMANN<sup>1,3</sup>;

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**Abstract:** The amygdala is a complex structure composed of thirteen nuclei that undergoes a protracted developmental trajectory, marked by increasing neuron numbers and expanding connectivity into adulthood. A key contributor to this prolonged growth is the paralaminar nucleus which contains a pool of immature neurons that mature and presumably migrate into the basal nucleus—an amygdala subregion highly interconnected with cortical regions and hippocampus. In autism spectrum disorder (ASD), the amygdala undergoes an atypical developmental trajectory characterized by an early excess of neurons and increased volume during childhood, followed by cell and spine loss in adulthood, particularly in lateral nucleus—the primary subregion for input into the amygdala. This study aims to identify developmental and inflammatory pathways that may contribute to this atypical growth in ASD by analyzing immune-related molecules, including cytokines, chemokines, and growth factors, and by mapping transcriptional profiles of neurons and glial cells within amygdala nuclei from postmortem brain tissue. This study included 34 age-matched cases (19 controls and 15 ASD) aged 12 to 46 years. Fresh-frozen samples were collected from the amygdala lateral, basal, and paralaminar nuclei. We employed a multi-omic approach, using multiplex assays on the Luminex platform to assess 1) transcriptomic expression (QuantiGene Plex) and 2) protein concentration (Milliplex Multiplex Assay). In ASD, AP-1 transcripts *JUN* and *JUNB* are elevated in paralaminar nucleus, along with *PDGFA* and *NCAM1*. Basal nucleus shows elevated *STAT1* and *TUBB3* gene expression. Chemokine eotaxin is decreased in both lateral and basal nuclei, while growth factors FGF-2 and PDGF-AA are selectively decreased in basal nucleus. Correlation matrices comparing transcript and protein levels revealed altered relationships in ASD, with multiple gene/protein correlations showing opposing patterns compared to controls. These altered correlations include significant links between neuronal maturation and neuroimmune signaling, indicating a potential role for the AP-1 pathway in amygdala development. Increased expression of AP-1 subunits, along with decreased levels of eotaxin and growth factors, point to disrupted immune signaling within specific nuclei. Differences in transcript-protein relationships suggest dysregulation of neuroinflammatory pathways. Together, these support a role for

neuroinflammation in shaping amygdala development and function in ASD, underscoring the need for further investigation into immune-related mechanisms that could inform therapeutic strategies.

**Disclosures:** E.C. Haley: None. E.L. Carlson: None. J. Van De Water: None. C.M. Schumann: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.14/A28

**Topic:** A.06. Developmental Disorders

**Support:** Genetic Autism Alliance

**Title:** Syt1 D366E mutation disrupts synaptic inputs and presynaptic targeting in cultured primary neurons

**Authors:** \*A. SAFAEI<sup>1</sup>, B. YU<sup>2</sup>, A. RAJOOLDEZFULY<sup>3</sup>, W. ARNOLD<sup>4</sup>, Z. WANG<sup>5</sup>, D.-P. LI<sup>7</sup>, P. R. CARNEY<sup>6</sup>, D. DAVIS<sup>2</sup>;

<sup>1</sup>Univ. of Missouri-Columbia (SSO), Columbia, MO; <sup>2</sup>Univ. of Missouri-Columbia, University of Missouri-Columbia, MO; <sup>3</sup>Univ. Of Missouri, Columbia, Columbia, MO; <sup>4</sup>NextGen Precision Hlth., <sup>6</sup>Child Hlth., <sup>5</sup>Univ. of Missouri, Columbia, Columbia, MO; <sup>7</sup>Med., Univ. of Missouri, Columbia, MO

**Abstract: SYT1 D366E mutation disrupts synaptic inputs and presynaptic targeting in cultured primary neurons.** Azadeh Safaei, Baocong Yu, Ali Rajooldezfuly, W. David Arnold, Zhonglei Wang, Daniel Davis, De-Pei Li, Paul R. Carney Affiliations: University of Missouri, Columbia **Abstract** Synaptotagmin 1 (SYT1) is a presynaptic protein sensing calcium signal to trigger calcium-dependent synchronous neurotransmitter release. Missense mutations in the calcium binding C2 domains are causative to SYT1-associated neurodevelopmental disorder (SYT1-NDD) and autistic symptoms. The disorder is characterized with early-onset behavioral, motor, and cognitive impairments due to disrupted synaptic transmission. This study aims to generate a cellular model with disease-associated D366E mutant SYT1 in cultured primary hippocampal neurons to show how these mutations alter synaptic function and presynaptic organization in developing neurons. Mouse primary hippocampal neurons were transfected by AAV9 constructs encoding human D366E mutant SYT1, human wild type SYT1 (WT SYT1), or empty vector. Whole-cell patch-clamp recordings from SYT1 D366E-transfected neurons revealed an increased frequency and reduced amplitude of miniature excitatory postsynaptic currents (mEPSCs) compared to both WT SYT1 and empty vector groups. Furthermore, the amplitude of sucrose-elicited EPSCs, which indicate readily releasable pool (RRP), decreased in D366E mutant SYT1 neurons compared to neurons transfected with WT SYT1 and empty vectors. However, transfection with D366E mutant SYT1 did not significantly alter evoked and

miniature inhibitory postsynaptic current (IPSCs), and sucrose-induced IPSCs in primary neurons. Immunocytochemical staining revealed that the colocalization of synaptophysin and SYT1 reduced in D366E mutant SYT1 compared to WT SYT1 and empty vector. These data suggest that D366E mutant SYT1 impairs evoked neurotransmitter release while increasing spontaneous neurotransmitter release. This model recapitulates core features of SYT1-NDD and provides a platform for further mechanistic and therapeutic exploration. **Keywords** SYT1 mutations, neurodevelopmental disorder, electrophysiology, hippocampal neurons, neurotransmitter release.

**Disclosures:** **A. Safaei:** A. Employment/Salary (full or part-time): University of Missouri Columbia. **B. Yu:** A. Employment/Salary (full or part-time): University of Missouri Columbia. **A. Rajooldezfuly:** A. Employment/Salary (full or part-time): University of Missouri Columbia. **W. Arnold:** A. Employment/Salary (full or part-time): University of Missouri Columbia. **Z. Wang:** A. Employment/Salary (full or part-time): University of Missouri Columbia. **D. Li:** A. Employment/Salary (full or part-time): University of Missouri Columbia. **P.R. Carney:** A. Employment/Salary (full or part-time): University of Missouri Columbia. **D. Davis:** A. Employment/Salary (full or part-time): University of Missouri Columbia.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.15/A29

**Topic:** A.06. Developmental Disorders

**Support:** NBRC Core Fund

**Title:** Regulation of homeostatic plasticity via proteome dynamics in rat models of autism

**Authors:** \*S. SULTANA, S. BANERJEE;  
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**Abstract:** Neurons maintain stable activity levels through homeostatic plasticity, adjusting synaptic strength and cellular excitability in response to prolonged increases in excitation or inhibition. Multiple studies have reported that homeostatic plasticity can induce changes in protein expression and post-translational modifications, altering the synaptic strength. However, the dynamic regulation of differentially expressed synaptic proteins during plasticity events and how these changes contribute to synaptic weights in autism remains poorly understood. In this study, we aim to identify proteins associated with homeostatic plasticity and their role in modulating synaptic strength. To achieve this, we induced homeostatic scaling in rat (P40) hippocampal slices using bicuculline stimulation for downscaling and tetrodotoxin (TTX) for upscaling, and proteomic profiling was performed using mass spectrometry (MS). To understand how specific proteins contribute to the regulation of synaptic strength during plasticity, we identified proteins uniquely expressed during upscaling or downscaling. Subsequently, an

interactome analysis of these proteins was conducted to investigate the potential signalling pathways involved in the homeostatic regulation of synaptic function. To further evaluate the role of these proteins in homeostatic plasticity, we used rat models of autism- Neurexin 1 (NRXN1) and Neuroligin 3 (NLGN3) knock-out to evaluate changes in their expression levels using MS. Additionally, to assess the activity-dependent functional differences, we performed patch-clamp recordings in all experimental models to measure changes in synaptic currents and network activity during upscaling and downscaling. This study seeks to elucidate the dynamic protein regulation underlying the mechanism of homeostatic plasticity.

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## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR200.16/A30

**Topic:** A.06. Developmental Disorders

**Support:** R01MH097236  
R21MH129806

**Title:** Synaptic density and transcriptional dysregulation reveal divergent E/I signaling patterns in the amygdala in ASD

**Authors:** \*M. DUONG<sup>1,3</sup>, E. L. CARLSON<sup>4,3</sup>, H. ZAKHARENKOV<sup>2,3</sup>, E. C. HALEY<sup>4,3</sup>, A. OMANSKA<sup>5</sup>, K. L. HANSON<sup>5,3</sup>, K. D. MURRAY<sup>6</sup>, C. M. SCHUMANN<sup>4,3</sup>;

<sup>1</sup>Univ. of California, Davis, Sacramento, CA; <sup>2</sup>California Natl. Primate Res. Ctr., Univ. of California, Davis, Davis, CA; <sup>3</sup>UC Davis MIND Inst., Sacramento, CA; <sup>4</sup>Cell Biol. and Human Anat., <sup>5</sup>Psychiatry and Behavioral Sci., Univ. of California, Davis, Sch. of Med., Sacramento, CA; <sup>6</sup>Physiol. and Membrane Biol., Univ. of California, Davis, Sch. of Med., Davis, CA

**Abstract:** Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by differences in social behavior and communication. The amygdala—a key brain region for emotion and social processing—follows a prolonged developmental trajectory and exhibits atypical structural and functional maturation in ASD. Emerging evidence points to alterations in both synaptic organization, reflected in the density of excitatory and inhibitory synaptic proteins, and in the expression of genes involved in neurotransmission. This study integrates analysis of synaptic protein density with transcriptomic profiling to examine potential patterns of convergence and divergence in the amygdala lateral and basal nuclei, primary input subregions with strong cortical connectivity, including to the prefrontal cortex and hippocampus. Using postmortem human brain tissue, we quantified inhibitory and excitatory synapse density via immunolabeling of GAD65/67 and PSD95, respectively, and analyzed with Fiji's Synapse Counter. Gene expression was evaluated using a QuantiGene Plex assay, a highly sensitive platform for measuring targeted gene levels, in addition to single-nucleus RNA sequencing to

evaluate cell type specific transcriptomic changes from 2 mm fresh-frozen tissue punches. RNAscope HiPlex v2 was used to spatially map expression of synaptic genes across nuclei at single-cell resolution. We observed increased inhibitory synapse density (GAD65/67+) in ASD cases in both lateral and basal nuclei. However, *GADI* transcript levels were reduced in the lateral nucleus. In contrast, excitatory synapse density (PSD95+) did not differ from controls, yet expression of excitatory genes *SLC17A7* and *DLG4* was significantly increased. These findings highlight a dissociation between synaptic protein abundance and gene expression, suggesting that altered transcription may not always reflect changes in synapse structure, and vice versa. The discrepancy may reflect compensatory mechanisms, wherein the brain attempts to adjust synaptic signaling to maintain functional balance in the context of broader circuit dysfunction. Given the extended maturation of the amygdala and its reciprocal connections with other brain regions such as the prefrontal cortex, these adaptations may reflect system-level responses to early developmental perturbations. By integrating multi-scale molecular data within spatial and cellular contexts, this study deepens our understanding of synaptic dysregulation in ASD and may help identify new intervention targets aimed at restoring balance in neural connectivity and signaling.

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## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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**Topic:** A.06. Developmental Disorders

**Support:** Autism Spectrum Program of Excellence, University of Pennsylvania  
NIMH Grant R01MH136354

**Title:** Cortical Kmt2c Haploinsufficiency Impairs Synaptic Transmission and is Associated with Autism-Related Behavioral Phenotypes in Mice

**Authors:** \*A. CHANDRA<sup>1</sup>, S. PANDEY<sup>2,4</sup>, K. CHOI<sup>5</sup>, Z. ZHOU<sup>3</sup>, M. V. FUCCILLO<sup>2,4</sup>;  
<sup>1</sup>Neurosci., Univ. of Pennsylvania, Philadelphia, PA; <sup>2</sup>Neurosci., <sup>3</sup>Genet., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA; <sup>4</sup>Autism Spectrum Program of Excellence, Philadelphia, PA; <sup>5</sup>Physiol., Hallym Univ., Chuncheon-si, Gangwon-Do, Korea, Republic of

**Abstract:** Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder frequently associated with mutations in genes implicated in synaptic function and chromatin regulation. Recent evidence suggests that these two genetic signals could converge at the level of neural circuit connectivity, with synapses having unique chromatin requirements that make them especially vulnerable to epigenetic dysregulation. Epigenetic mechanisms, including chromatin remodeling, are critical for orchestrating spatial and temporal patterns of gene expression during

brain development. Kmt2c encodes a histone methyltransferase responsible for H3K4 methylation and has been implicated in ASD; however, its role in cortical circuit assembly and behavior remains unclear. Here, we examined the effects of cortical Kmt2c heterozygous deletion on cortical circuit development and behavior in mice. Electrophysiological recordings from acute brain slices revealed a significant reduction in excitatory synaptic transmission within the cortico-striatal pathway in Kmt2c heterozygous mice compared to wild-type littermates. Immunohistochemical analysis showed a decreased ratio of vGluT1 to vGluT2 puncta density in the dorsomedial striatum (DMS), suggesting deficits in cortico-striatal synaptogenesis or maintenance. We analyzed the patterns and statistics of spontaneously generated motor behavior using non-supervised behavioral classifiers. Mutant mice exhibited increased locomotor activity, reduced grooming, and shortened pausing behavior. Analysis of the higher-level structure of spontaneous behavior is ongoing. These findings demonstrate that Kmt2c regulates presynaptic organization and excitatory input to the striatum, supporting a mechanistic link between epigenetic dysregulation, synaptic alterations, and neurodevelopmental pathology.

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## **Poster**

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**Title:** Foxp1-dependent development of drd2-expressing spiny projection neurons underlies striatal circuit formation

**Authors:** \*N. KHANDELWAL, A. A. KULKARNI, G. KONOPKA, J. R. GIBSON;  
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**Abstract:** Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by communication and behavior deficits. Among the brain regions implicated in ASD, the striatum plays a central role in manifesting the motor and speech abnormalities, as well as the repetitive behaviors, often observed in affected individuals. We investigated the regulatory function of a high-confidence, ASD-associated transcription factor - FOXP1, in striatal development and its impact on corticostriatal circuitry to understand the underlying pathophysiology. The striatum is primarily composed of two distinct GABAergic spiny projection neurons (SPNs), categorized

into D1 and D2 subtypes. Our preliminary findings indicate that FOXP1 plays a neuron subtype-specific role, particularly in the development of D2 SPNs. Using a transgenic mouse model with embryonic deletion of *Foxp1* specifically in D2 SPNs, we observed a significant reduction in the number of these neurons. To elucidate the mechanisms underlying this loss and the role of FOXP1 in maintaining the normal number of D2 SPNs, we performed single-nucleus RNA sequencing (snRNA-seq) of the striatum across multiple developmental stages. Our transcriptomic analyses suggest that the reduced number of D2 SPNs in *Foxp1*-deficient mice may be due to compromised differentiation of neural progenitor cells as well as increased neuronal death. Furthermore, we identified that FOXP1 is essential for the survival of a specific subpopulation of D2 SPNs during their early postnatal development. These findings provide new insights into how FOXP1 contributes to striatal development and ASD pathophysiology, potentially opening avenues for targeted therapeutic interventions.

**Disclosures:** N. Khandelwal: None. A.A. Kulkarni: None. G. Konopka: None. J.R. Gibson: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.19/A33

**Topic:** A.06. Developmental Disorders

**Support:** NIH-R01 GM135087  
NIH-F31 NS132473-01A1

**Title:** Sensory neocortical circuit dysfunction in a mouse model of *Setd2* haploinsufficiency

**Authors:** \*A. POPE<sup>1</sup>, M. CREWE<sup>2</sup>, L. HEADY<sup>6</sup>, J. D. RICHTER<sup>7</sup>, R. MADABHUSHI<sup>3</sup>, J. R. GIBSON<sup>4</sup>, K. M. HUBER<sup>5</sup>;

<sup>1</sup>Neurosci., UT Southwestern Neurosci. Grad. Program, Dallas, TX; <sup>3</sup>Psychiatry, <sup>4</sup>Dept. of Neurosci., <sup>5</sup>Neurosci., <sup>2</sup>UT Southwestern Med. Ctr., Dallas, TX; <sup>6</sup>Univ. of Texas Southwestern Med. Ctr., Dallas, TX; <sup>7</sup>UMass Med. Sch., Amherst, MA

**Abstract:** In neurons, dysregulation of histone methylation is associated with neurodevelopmental disorders such as autism spectrum disorders (ASD). SET Domain Containing 2, histone lysine methyltransferase (SETD2) methylates histone H3 at lysine 36 (H3K36) and is the primary trimethyltransferase for H3K36 in human (H3K36me3). *SETD2* is also considered a “high confidence” ASD-risk gene and haploinsufficiency of *SETD2* is responsible for Sotos-like overgrowth syndrome. Little is known about the role of SETD2 and H3K36me3 in postnatal developing brain. To address these gaps in knowledge, I made a mouse with conditional deletion of *Setd2* postnatally (~P8) in excitatory forebrain neurons using the BAC-CaMKII $\alpha$  Cre line. Acute slices of somatosensory neocortex from young, 3<sup>rd</sup> postnatal week, *Setd2* heterozygous mice (*Setd2* cHet) showed increased circuit excitability, as measured

by the duration and power of persistent activity (UP) states. A cellular substrate for circuit hyperexcitability in *Setd2* cHet may be a deficit in inhibitory synaptic transmission that is observed as a ~50% decrease in spontaneous, miniature (m) IPSC frequency onto *Setd2* cHet Layer (L) 2/3 pyramidal cortical neurons. Both long duration UP states and reduced mIPSC frequency are corrected by preincubation of *Setd2* cHet slices in either an mGluR5 negative allosteric modulator, MTEP, cannabinoid receptor 1 (CB1R) antagonist, Rimonabant, or inhibitors of protein synthesis. Importantly, these inhibitors have no effect on UP states or mIPSC frequency on wildtype L2/3 neurons. These results suggest that *Setd2* deletion leads to an aberrant mGluR5-, CB1R- and protein synthesis-dependent suppression of inhibitory synaptic transmission that in turn leads to hyperexcitability of local cortical circuits. Remarkably, we have previously observed an mGluR5/CB1R-dependent cortical hyperexcitability and suppression of inhibitory synaptic transmission in the mouse model of Fragile X Syndrome (*Fmr1* KO). Together our results suggest that *Fmr1* and *Setd2* commonly regulate processes that affect mGluR5/CB1R function. Ongoing efforts are focused on determining the altered transcriptome and H3K36me3 in *Setd2* cHet cortex and if there are any molecular changes in common with the *Fmr1* KO.

**Disclosures:** A. Pope: None. M. Crewe: None. L. Heady: None. J.D. Richter: None. R. Madabhushi: None. J.R. Gibson: None. K.M. Huber: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.20/A34

**Topic:** A.06. Developmental Disorders

**Support:** NIH Grant: 1R56MH130599-01A1

**Title:** Altered Distribution of Perineuronal Nets in the *Arid1b* Haploinsufficient Brain Across Development

**Authors:** \*J. M. ACKERMAN<sup>1</sup>, S. KATTEWAR<sup>2</sup>, T. FORD<sup>2</sup>, W.-Y. KIM<sup>2</sup>;

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**Abstract:** Haploinsufficiency of the *AT-Rich Interactive Domain 1B* (*ARID1B*) gene causes autism spectrum disorders (ASD). However, the cellular and molecular mechanisms underlying *ARID1B* haploinsufficiency in the brain remain poorly understood. Our previous study has shown that the genesis, maturation, and function of Parvalbumin (PV) interneurons are impaired in a mouse model of *ARID1B* haploinsufficiency. Perineuronal Nets (PNNs) are an extracellular matrix structure essential for PV neuron maturation and function. They are also associated with sex-dependent phenotypes in the brain. Thus, we investigated whether PNNs are linked to *ARID1B* haploinsufficiency-induced neurodevelopmental abnormalities, with a specific focus on their distribution around PV neurons. Using immunohistochemistry and stereological



quantification, we found that there is a reduction in the number of PNNs surrounding PV neurons in the *Arid1b* haploinsufficient brain across developmental stages. Furthermore, the reductions in both the colocalization of PV/PNN and total PNN number were less severe in females. This sex-specific difference is particularly noteworthy given the sexual dimorphism observed in ASD, as males are nearly four times more likely to be diagnosed than females. Our data suggests that PNNs may have a crucial role in PV interneuron development and may offer a neuroprotective effect in females, potentially explaining the unequal ratios in ASD diagnoses between sexes.

**Disclosures:** J.M. Ackerman: None. S. Kattewar: None. T. Ford: None. W. Kim: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.21/A35

**Topic:** A.06. Developmental Disorders

**Title:** Oligodendroglial participation in an autism model: relationship with interoceptive connectivity

**Authors:** \*K. COLIN<sup>1</sup>, D. V. CASTILLO<sup>2</sup>;

<sup>1</sup>Univ. Autónoma del Estado de Morelos, Cuernavaca, Mexico; <sup>2</sup>UAEM, Cuernavaca, Mexico

#### **Abstract: Oligodendroglial participation in an autism model: Relationship with interoceptive connectivity Authors Karina Colin, Diana V, Castillo. Abstract**

During foetal and postnatal development, intricate glial mechanisms orchestrate the formation of appropriate anatomical and functional brain connectivity. In Autism Spectrum Disorder (ASD), disrupted interoceptive processing a fundamental system for internal bodily awareness and emotional regulation has increasingly been recognised as a key factor underlying social and affective difficulties. The transcription factor Olig2, essential for oligodendrocyte maturation and myelination, has been implicated in ASD pathophysiology through its role in demyelination and impaired neural communication. This study investigates the role of Olig2 in altered interoceptive connectivity, focusing on the insular cortex-basolateral amygdala pathway, which is critical for integrating sensory and emotional information. A valproic acid (VPA)-induced rat model of autism was used, with gestational exposure on embryonic day 12.5. Key postnatal windows for oligodendroglial development (postnatal days 10-22) were analysed. Recombinant growth hormone (GH), known to modulate IGF-1 levels and promote myelinogenesis, was administered to assess its potential restorative effects on oligodendrocyte maturation and functional connectivity. Functional interoceptive connectivity was evaluated through in vivo long-term potentiation (LTP) recordings within the amygdala-insula circuit, while immunohistochemical analyses measured expression levels of Olig2, IGF-1, c-Fos, and myelin markers. Behavioural assays targeted interoception-related emotional regulation, fear conditioning, repetitive behaviours, and locomotion. This integrative approach seeks to elucidate how oligodendroglial dysfunction and impaired myelination contribute to interoceptive disconnection and emotional

dysregulation in ASD, proposing hormonal therapies as a potential strategy to restore brain connectivity and alleviate core symptoms.

**Disclosures:** K. Colin: None. D.V. Castillo: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.22/A36

**Topic:** A.06. Developmental Disorders

**Support:** Families SCN2A

**Title:** Characterization and therapeutic restoration of sodium channel models for autism spectrum disorder

**Authors:** \*A. AL SANEH<sup>1</sup>, L. GISSOT<sup>1</sup>, M. O'BRYAN<sup>1</sup>, K. KRUTH<sup>2</sup>, A. J. WILLIAMS<sup>2</sup>, C. AHERN<sup>1</sup>;

<sup>1</sup>Mol. Physiol. and Biophysics, <sup>2</sup>Psychiatry, Univ. of Iowa, Iowa City, IA

**Abstract:** Autism spectrum disorder (ASD) is estimated to occur in one out of every 36 children. The understanding of the mechanism behind ASD remains limited largely due to the disorder's remarkably complex etiology. Roughly five percent of ASD cases are monogenic in origin and can be traced to a single causal genetic variation. The highest monogenic ASD risk gene is *Scn2a*, where premature termination codons (PTC) truncate the encoded protein, the sodium channel Nav1.2. Nonsense mutations leading to the abortive translation of the *Scn2a* gene result in reduced social interactions and repetitive behaviors as well as ataxia and cerebellar atrophy. Unfortunately, there are currently no *Scn2a* PTC mouse models available for autism research that would otherwise enable research avenues and therapeutic strategies. We have developed two *Scn2a* PTC mouse models (Tyr84X and Arg1626X), which are the first PTC autism rodent models to date. These mice are specific genetic models of ASD-linked *Scn2a* mutations that address specific differences in genotype-phenotype relationships. Given the broad context of their positions within the *Scn2a* gene, PTC mutations represent a significant challenge. Small molecule "read-through" therapies, for instance, have performed poorly in clinical trials and next generation gene editing approaches require specific validation for hundreds of individual somatic *Scn2a* PTC loci. To fill this gap, we have developed an approach using anticodon-edited transfer RNA (tRNA) to repair in-frame termination codons. We have previously developed a platform of anti-codon modified human tRNAs to identify multiple tRNA types for every known human PTC disease variant. By packaging the codon-edited tRNA into virus, we show its therapeutic potential upon delivery into induced pluripotent stem cells (iPSCs) from patients with *Scn2a* PTC variants as well as *in vivo* mouse models. Using ribosomal profiling and mass spectrometry we have found that expressed suppressor tRNAs have minimal contact with native stop codons. Further, through quantitative RNA methods, we show that SCN2a PTC mRNAs display modest

nonsense mediated decay. In conclusion, the complexity of ASD and its genetic underpinnings, particularly the role of the *Scn2a* gene, necessitate innovative research approaches. The development of the first PTC autism rodent models, Tyr84X and Arg1626X, marks a significant step forward in this field. Moreover, the novel use of anticodon-edited transfer RNA (tRNA) to repair in-frame termination codons offers a promising therapeutic strategy. This approach paves the way for future research and potential treatments for many PTC-associated diseases, well beyond ASD.

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## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.23/A37

**Topic:** A.06. Developmental Disorders

**Support:** NSF GRFP  
UCSF Discovery Fellows Program  
FamilieSCN2A Action Potential Award  
FamilieSCN2A Hodgkin Huxley Award  
SFARI 4551

**Title:** *Scn2a* haploinsufficiency induces cortical hyperexcitability and increases seizure susceptibility in long-evans rats

**Authors:** \*S. E. TALOMA<sup>1</sup>, M. E. COULTER<sup>4</sup>, K. A. SALVATI<sup>2</sup>, R. NEVERS<sup>1</sup>, R. ALEXANDER<sup>1</sup>, E. HAMADA<sup>5</sup>, B. SHARMA<sup>5</sup>, G. WILLIAMS<sup>1</sup>, D. B. KASTNER<sup>6</sup>, A. GONZALEZ-SULSER<sup>7</sup>, L. M. FRANK<sup>8</sup>, K. J. BENDER<sup>3</sup>;

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**Abstract:** Genetic variation in *SCN2A* is a major risk factor for neurodevelopmental disorders, including developmental epilepsies, autism spectrum disorder (ASD), and intellectual disability. *SCN2A* encodes the voltage-gated sodium channel Nav1.2, which in mature neocortex, is expressed primarily in excitatory neuron dendrites. Loss-of-function (LoF) variants that suppress or eliminate Nav1.2 function are associated with intellectual disability and ASD, and, in an estimated 20-30% of children, epilepsy with onset after the first 3 months of postnatal development. Our goal here is to understand how loss of Nav1.2 in excitatory neurons affects seizure susceptibility. Long-Evans rats heterozygous for the *Scn2a* gene have been developed as a

model for studying effects of Nav1.2 loss. We find that these animals exhibit spontaneous seizure-like events as assayed by local field potential (LFP) recordings from the corpus callosum and multi-site electroencephalogram (EEG) recordings from the cortical surface. Specifically, we observed an increase in spike-wave discharges (SWDs) in *Scn2a*<sup>+/-</sup> rats relative to wild type littermate controls. These SWDs occurred most frequently during periods of rest, leading to fractured sleep. Consistent with cortical hyperexcitability *in vivo*, we observed increased excitability of pyramidal cells *ex vivo*, measured by increased AP frequency for any given somatic current injection stimulus. This appears to be due to two mechanisms: first, the loss of Nav1.2 in neocortical pyramidal cell dendrites leads to a lack of depolarization-dependent engagement of dendritic voltage-gated potassium channels. As such, neurons do not repolarize as effectively between APs, priming them for subsequent activity. Second, these neurons have increased input resistance, and further electrophysiological analysis suggests that potassium channel function in dendrites is reduced. Thus, direct interactions between Nav1.2 and dendritic potassium channels, and long-term changes in dendritic potassium channel function due to heterozygous loss of Nav1.2, may increase seizure burden in rat models. As such, we have begun testing anti-epileptic drugs (AEDs) for efficacy in the *Scn2a*<sup>+/-</sup> rats, as well as their susceptibility to chemical convulsants. This work aims to establish a mechanistic link between loss of Nav1.2 and seizure generation, providing a new model to understand *Scn2a* loss-of-function related epilepsies and evaluate therapeutics.

**Disclosures:** S.E. Taloma: None. M.E. Coulter: None. K.A. Salvati: None. R. Nevers: None. R. Alexander: None. E. Hamada: None. B. Sharma: None. G. Williams: None. D.B. Kastner: None. A. Gonzalez-Sulser: None. L.M. Frank: None. K.J. Bender: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.24/A38

**Topic:** A.06. Developmental Disorders

**Title:** Dissecting the Molecular Mechanism of Rare NLGN3 Variants

**Authors:** \*K. HOSSAIN;

Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD

**Abstract:** A commonly disrupted protein network in NDDs includes genes encoding synaptic proteins involved in functions such as synaptic adhesion (e.g., NLGNs and NRXNs), receptor localization and function, synaptic vesicle release, and postsynaptic scaffolding. In these disorders, missense mutations often impair channel or receptor activity, alter post-translational modification sites (such as phosphorylation or glycosylation), or disrupt binding interfaces. These alterations compromise the precise regulation of protein domains, affecting overall protein function and associated signaling pathways. Neuroligins (NLGNs) are postsynaptic adhesion molecules essential for neuronal development and have been implicated in neurodevelopmental

disorders (NDDs). In humans, five genes encode the NLGN family of proteins. These are single-pass transmembrane proteins characterized by a large extracellular acetylcholinesterase-like domain and a short intracellular tail. NLGNs localize to the postsynaptic density, where they play a crucial role by interacting with presynaptic neuroligins (NRXNs). To identify critical subdomains within the NLGN gene family, our lab developed an algorithm that evaluates tolerance to missense mutations by comparing clinical variants from ClinVar with reference variants from gnomAD. Using this approach, we identified a cluster of four NLGN3 variants associated with NDDs. One variant, V204A, was found in 27 out of 108 children diagnosed with autism spectrum disorder. Our studies indicate that two of the four identified variants result in trafficking deficits when expressed in HEK cells. Notably, the NLGN3 V204F and V204A variants exhibit impaired maturation and increased endoplasmic reticulum (ER) retention. When expressed in HeLa cells, these variants also show impaired surface trafficking. Ongoing studies are assessing trafficking and synapse localization in neurons as well as binding to presynaptic NRXNs. These investigations will provide further insight into the mechanisms of neuronal dysfunction observed in patients with rare variants in this newly identified cluster.

**Disclosures: K. Hossain:** None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.25/A39

**Topic:** A.06. Developmental Disorders

**Title:** Characterization of NLGN3 Clinical Variants Identified via Analysis of Genetic Variants Clustering

**Authors:** \*A. W. LEHR<sup>1</sup>, K. W. ROCHE<sup>2</sup>;

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**Abstract:** Neuroligins (NLGNs) are single-pass transmembrane proteins, localizing to the postsynaptic density where they bind presynaptic neuroligin (NRXN), acting as postsynaptic adhesion molecules. Some of the earliest familial genetic studies reveal NLGN mutations associated with neurodevelopmental disorders (NDDs), implicating a critical role for NLGNs in neuronal development. Broadly within NDDs, mutations in genes encoding synaptic proteins, converge on protein networks that mediate functions such as synaptic contact/adhesion (NLGN, NRXN), synaptic vesicle release, post-synaptic scaffolding, and receptor localization. NDD-associated missense mutations have been shown to disrupt receptor/channel function, binding interfaces, or post-translational modification sites like phosphorylation or glycosylation, abolishing the temporal and spatial control these domains exert over the protein, and their broader signaling pathways. To identify critical protein subdomains within the NLGN gene family, I developed an algorithm that assesses tolerance to missense mutations in human genetic variation by comparing clinical variants from ClinVar to reference variants from gnomAD.

(unimpacted control variants). Within the globular structured domain of NLGNs, there are three sensitive regions prominently enriched in clinical variants. These regions coincide with subdomains that underlie critical functions for NLGNs, such as within glycosylation, NRXN-binding, and dimerization, implicating these variants as structurally disrupting critical protein folding, and thus function. These genetic analyses identified a previously reported cluster of pathogenic variants in NLGN4X, confirming its validity in identifying sensitive regions. Interestingly, we find analogous sensitivity in NLGN1 and NLGN3, aligning with the identified NLGN4X cluster. It is also reassuring that the algorithm identifies a region around the highly characterized NLGN3 R451C (R471C in humans) NDD-associated mutation, highlighting several uncharacterized variants (A462T, R470C, L477F) within this cluster. These variants phenotypically copy NLGN3 R451C in *in vitro* experimental findings, with a reduction in protein stability and surface expression. The current literature suggests divergent etiological pathways for NLGN3 R451C NDD phenotypes; reduction in NLGN3 expression leads to gain of function effects, or NLGN3 misfolding leads to ER stress inducing neuronal death. I will compare NLGN3 heterozygous knockout mice versus NLGN3 homozygous/hemizygous R451C to dissect stoichiometry versus ER-stress importance in NLGN3's role in NDDs.

**Disclosures:** A.W. Lehr: None. K.W. Roche: None.

## **Poster**

### **PSTR200: Autism: Synaptic and Cellular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR200.26/A40

**Topic:** A.06. Developmental Disorders

**Support:** 1ZIAN003140-09

**Title:** Pathogenic NLGN4X variants reveal dual roles in synaptic connectivity and cortical development

**Authors:** \*E. HONG<sup>1</sup>, M. E. REYES-MENDEZ<sup>2</sup>, C. GUISSART<sup>3</sup>, A. KAPOOR<sup>4</sup>, J. D. BADGER<sup>1</sup>, W. LU<sup>2</sup>, K. W. ROCHE<sup>1</sup>;

<sup>1</sup>Receptor Biol. Section, NINDS, Bethesda, MD; <sup>2</sup>Synapse and Neural Circuit Res. Section, NIH/NINDS, Bethesda, MD; <sup>3</sup>Lab. de Biochimie et Biologie Moléculaire, Univ. of Montpellier, Nîmes, France; <sup>4</sup>NIH/NCATS, Rockville, MD

**Abstract:** Neurodevelopmental disorders (NDDs) influence brain functions and neurological development, causing difficulties in social, cognitive, and emotional functioning. Numerous genes have been identified as potential contributors to NDDs based on both human genetics and etiological evidence. Among these genes, the neuroligins (NLGN1-3, NLGN4X, and NLGN4Y) have emerged as strongly linked to NDDs. NLGNs are postsynaptic cell adhesion molecules that interact with presynaptic neurexins (NRXNs) and play a crucial role in neuronal development, synaptic transmission, and synaptic plasticity. Within the NLGN family, NLGN4X stands out

with the highest number of variants associated with NDDs. Most of these rare variants are located within the extracellular esterase homology domain, and these mutations lead to issues with surface expression and impaired neuronal function. Notably, multiple variants within the first 100 amino acids of NLGN4X (Nguyen et al., Neuron, 2020) display trafficking defects. In this study, we have identified NDD-associated NLGN4X variants located slightly downstream of previously characterized pathogenic hotspots (Nguyen et al., 2020). Structural modeling suggests that these variants destabilize the conformation of the protein. We find that these NLGN4X variants exhibit severe trafficking defects, leading to impaired cell surface localization and synaptogenesis by biochemical, imaging, and electrophysiological approaches. Importantly, we also provide the first in vivo evidence that NLGN4X contributes to neuronal migration, revealing an unexpected function of this synaptic protein in early brain development. Together, these results reveal that NDD-associated NLGN4X variants disrupt both synapse formation and neuronal migration, providing mechanistic insight into how NLGN4X mutations contribute to the neurodevelopmental pathology. This discovery sheds light on the structure/function relationship of NDD variants and provides valuable insights into potential therapeutic targets for individuals affected by this condition.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.01/A41

**Topic:** A.06. Developmental Disorders

**Title:** Maternal immune activation leads to activated proinflammatory response and reduction in MeCP2 levels in adult offspring

**Authors:** \*D. BEGMATOVA, A. PINHASOV;  
Ariel Univ., Ariel, Israel

**Abstract:** Maternal immune activation (MIA) during pregnancy is a well-established risk factor for neuropsychiatric disorders, including schizophrenia, bipolar disorder, and autism spectrum disorder. However, individual differences in stress resilience may modulate the impact of MIA on offspring neurodevelopment. Here, we investigate the interaction between MIA and inherited stress vulnerability using a selectively bred mouse model of dominant (stress-resilient) and submissive (stress-vulnerable) phenotypes. Pregnant mice were exposed to Poly(I:C) on gestational day 14, and offspring were assessed for neuroinflammatory, epigenetic, and behavioral alterations in adulthood. Our findings reveal a significant increase in IL-6 levels following Poly(I:C) administration, with submissive dams exhibiting a more pronounced inflammatory response. Prenatal MIA altered hippocampal expression of key DNA methylation-related enzymes, including a significant reduction in MeCP2 levels in adult offspring,

particularly in the stress-vulnerable subgroup. Furthermore, MIA-induced changes in glutamatergic and dopaminergic neurotransmission were reflected in enhanced MK-801 sensitivity and deficits in long-term memory in submissive offspring. These neurochemical and behavioral alterations provide mechanistic insight into how MIA contributes to psychiatric vulnerability. Critically, our results suggest that stress resilience modulates the long-term consequences of prenatal immune activation, highlighting potential biomarkers for identifying at-risk individuals. Given the central role of MeCP2 in neurodevelopmental and psychiatric disorders, our findings may inform future therapeutic strategies targeting epigenetic and neuroimmune pathways to mitigate MIA-induced neuropsychiatric risk.

**Disclosures:** D. Begmatova: None. A. Pinhasov: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.02/A42

**Topic:** A.06. Developmental Disorders

**Support:** NIH Grant RO1 MHI35390

**Title:** Maternal immune activation leads to enduring cell-specific transcriptomic changes in the brain of Rhesus macaque offspring

**Authors:** \*E. CARLSON<sup>1,3</sup>, S. KAMBOJ<sup>2,4</sup>, A. S. FOX<sup>2,4</sup>, M. D. BAUMAN<sup>5,3,4</sup>, C. M. SCHUMANN<sup>3,1</sup>;

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<sup>4</sup>California Natl. Primate Res. Ctr., Davis, CA; <sup>5</sup>Physiol. and Membrane Biol., Univ. California, Davis, Sacramento, CA

**Abstract:** A robust maternal immune response during pregnancy can alter the trajectory of offspring brain development and increase the likelihood of neurodevelopmental disorders. In a nonhuman primate model of maternal immune activation (MIA), we found prenatal immune challenge can result in subtle but significant changes in offspring social development that implicates functional changes in the amygdala. We expanded this investigation to a larger cohort of 26 Rhesus macaque offspring—14 saline and untreated controls, 12 MIA-exposed with Poly:IC/LC in the first trimester. Using single nucleus RNA sequencing (snRNA-seq), we targeted 10,000 nuclei/case/region from 3 individual amygdala subnuclei (lateral, accessory basal, and central) and evaluated cell specific gene expression. Neurons and astrocytes across all three regions consistently have the highest numbers of differentially expressed genes (DEGs), and the majority of transcripts are downregulated in MIA. We next performed GO Enrichment Analysis on the DEG lists and identified changes to biological processes. Several dysregulated processes are shared across multiple regions and clusters and include pathways involved with



axon guidance, synaptic structure, ion regulation, and cell projection/motility. Subsequently, we ran RNAscope HiPlex V2 on sections from a subset (5 control, 5 MIA) of cases to gain insight in the spatial distribution of key DEGs associated with axon guidance (UNC5C, SLIT1), synaptic architecture (NRXN1, NRXN3, SHANK3, NLGN2), immune function (IL1RAP, IL6R), and also included cell-type identifying probes SLC17A7 (excitatory neurons), GAD1 (inhibitory neurons), AQP4 (astrocytes), and ITGAM (microglia). Expression changes suggestive of altered connectivity and neurotransmission are evident in the primate amygdala 4 years after prenatal exposure to an activated maternal immune system and this has profound implications for the etiology of neurodevelopmental and psychiatric disorders. While the disruption to multifaceted elements of neurotransmission-related expression is striking, it is important to note that this data set represents a single point of time, and future research is needed to determine the trajectory of transcriptomic changes across development.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.03/A43

**Topic:** A.06. Developmental Disorders

**Support:** P50MH106438-6618  
P50MH106438-6616

**Title:** Maternal immune activation is associated with lower white matter micro-organization in rhesus macaques (*Macaca mulatta*) at pre-puberty

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**Abstract:** Translational research has shown that prenatal exposure to maternal immune activation (MIA) can increase the risk of neurodevelopmental disorders (NDDs) in offspring. Nonhuman primate models, due to their neuroanatomical similarity to humans, are uniquely valuable for investigating how MIA impacts brain development. Prior studies in rhesus macaques have demonstrated that MIA-exposure can result in phenotypes relevant to schizophrenia and other NDDs, including cognitive impairments, altered dendritic morphology, elevated striatal dopamine, reduced prefrontal, and frontal gray matter volumes, and increased

extracellular free water in the cingulate cortex. However, the effects of MIA on white matter (WM) development remain less understood. We present longitudinal diffusion MRI data examining WM micro-organization in male offspring born to rhesus macaques exposed to MIA during the late first trimester, compared to controls (CON). Imaging was conducted at 6, 12, 24, 36, and 45 months. Diffusion tensor imaging (DTI) data were processed using the UNC-Utah NA-MIC DTI fiber tract analysis framework. We used piecewise linear mixed models with a single age knot to model the relationship between age and fractional anisotropy (FA) and assess group differences in developmental trajectories. No group differences in FA were observed between 6 and 24 months. However, starting at 24 months, MIA and CON groups showed diverging trajectories, with significantly lower FA at 36 and 45 months in MIA-exposed offspring. Significant age-by-group interactions were detected in three WM tracts: the frontal segment of the corpus callosum (cc1d) ( $p = 0.002$ ), and the left (cg\_l) and right cingulum bundles (cg\_r) ( $p = 0.015$  and  $p = 0.013$ , respectively). Other DTI scalars (e.g., radial diffusivity) did not show significant group effects. Associations were examined between FA at 45 months in cc1d, cg\_l, and cg\_r and performance on the Intra-/Extradimensional Shift (ID/ED) task at 46-47 months. A significant association was found between extradimensional shift performance and FA in the cg\_r ( $r_s = 0.65$ ,  $p = 0.0005$ ), and cg\_l ( $r_s = 0.49$ ,  $p = 0.002$ ), suggesting that MIA-related white matter alterations may underlie cognitive flexibility impairments observed at pre-puberty.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR201.04/A44

**Topic:** A.06. Developmental Disorders

**Support:** RO1MH097236  
R21MH119650  
R21MH129806  
RO1MH125390

**Title:** Differential expression of synaptic genes in the amygdala: comparing autism spectrum disorder and nonhuman primate models of maternal immune activation

**Authors:** \*H. C. ZAKHARENKO<sup>1</sup>, E. CARLSON<sup>3</sup>, E. C. HALEY<sup>6</sup>, M. DUONG<sup>4</sup>, B. P. ANDER<sup>2</sup>, K. L. HANSON<sup>7</sup>, S. KAMBOJ<sup>5</sup>, K. D. MURRAY<sup>8</sup>, A. S. FOX<sup>9</sup>, M. D. BAUMAN<sup>10</sup>, C. M. SCHUMANN<sup>11</sup>;

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California Davis Neurosci. Grad. Group, Sacramento, CA; <sup>7</sup>UC Davis MIND Inst., Sacramento, CA; <sup>8</sup>Physiol. and Membrane Biol., Univ. California Davis, Davis, CA; <sup>9</sup>Psychology, Univ. of California - Davis, Davis, CA; <sup>10</sup>Univ. California, Davis, Sacramento, CA; <sup>11</sup>Dept. of Psychiatry, UC Davis Sch. of Medicine, MIND Inst., Sacramento, CA

**Abstract:** Children prenatally exposed to maternal infection have an increased risk of neurodevelopmental disorders, such as autism spectrum disorder (ASD) and schizophrenia. Nonhuman primate (NHP) models of maternal immune activation (MIA) demonstrate that the maternal immune response can lead to long-term changes in brain development and behavior in offspring. These changes include alterations in socioemotional development, which implicate disruptions to core functions of the amygdala. Identifying cell-specific transcriptional changes in the amygdala may serve as a crucial translational bridge for understanding associations between MIA and the risk of neurodevelopmental disorders.

A previous single nucleus RNA sequencing (snRNA-seq) study in amygdalas from MIA-exposed 4 year old NHP offspring revealed significant dysregulation in genes linked to synaptic structure and function overlapping with risk genes associated with ASD. We aim to explore the relationship between amygdala synaptic gene dysregulation in MIA-exposed offspring and human neurodevelopmental disorders.

We measured the expression of targeted synaptic genes (NRXN1, SHANK2, HOMER1, SHANK3) across both our NHP MIA model and postmortem human ASD and control brain tissue using the QuantiGene Plex Assay kit. We then used RNAscope HiPlex v2 on human and NHP amygdala sections to map synapse-related transcripts across cell types.

In the amygdala of individuals with autism, the expression of genes associated with synaptic function and risk of ASD is significantly upregulated. However, synaptic genes in MIA are largely downregulated for many of these same transcripts. Differential gene expression across both species can indicate synaptic dysregulation, which is known to impact neurodevelopment and neural function. Synaptic dysregulation across various cell types, such as excitatory and inhibitory neurons, could be involved in the disruption of synaptic tone, a critical factor for neurotypical development and brain function. In the amygdala, these changes could influence key socioemotional behavior deficits related to ASD. Knowledge of the molecular and cell type changes associated with neurodevelopmental disorders such as ASD enables us to better focus future research on their underlying mechanisms.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.05/A45

**Topic:** A.06. Developmental Disorders

**Support:** AT011162

**Title:** Does prenatal/perinatal acetaminophen treatment inhibit diacylglycerol lipase alpha to cause ASD-like behaviors in mice?

**Authors:** \*M. DVORAKOVA, E. SODUNKE, A. STRAIKER, K. MACKIE;  
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**Abstract:** Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition marked by impairments in social interaction, communication, and sensory processing, frequently accompanied by repetitive behaviors. While ASD etiology involves genetic and environmental components, accumulating evidence implicates prenatal exposure to acetaminophen (APAP) as a potential environmental risk factor. APAP is used by more than 50% of pregnant individuals, and epidemiological studies associate its use with increased ASD incidence, possibly through mechanisms involving oxidative stress and immune dysregulation. However, the neurobiological basis of APAP's influence on brain development remains poorly defined. Our recent work identifies a novel mechanism by which APAP may increase ASD risk: inhibition of diacylglycerol lipase alpha (DAGLa), the principal enzyme responsible for synthesis of the endocannabinoid 2-arachidonoylglycerol (2-AG). DAGLa is critical for central nervous system development, particularly in modulating axonal growth and guidance. Since disrupted axon pathfinding is implicated in ASD, inhibition of DAGLa by APAP offers a plausible mechanistic link. Additionally, clinical studies report altered endocannabinoid signaling in ASD patients, including reduced cannabinoid receptor 1 (CB1) expression and decreased circulating 2-AG levels. To test our hypothesis that APAP-induced DAGLa inhibition contributes to ASD-like phenotypes, we administered APAP to pregnant and lactating mouse dams and assessed behavioral outcomes in their offspring. Treated offspring exhibited altered ASD-related behaviors. Moreover, some of the latered behaviors were rescued by a chemogenetic approach that increased prefrontal cortex interneuron activity. Our findings suggest that APAP perturbs developmental endocannabinoid signaling by inhibiting DAGLa, thereby impacting neural circuit formation and contributing to ASD-relevant phenotypes. These results support a novel mechanistic link between APAP exposure during pregnancy and ASD risk.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.06/A46

**Topic:** A.06. Developmental Disorders

**Support:** R15S088776

**Title:** The Effect of Rapamycin and Minocycline treatment on autistic-like behavior in C57Bl/6J Mice after Early-Life Seizures

**Authors:** \*S. PELL<sup>1</sup>, K. BLANDIN<sup>2</sup>, T. BRADISH<sup>1</sup>, M. WALLIS<sup>1</sup>, C. KELLEY<sup>1</sup>, J. J. THAYIL<sup>1</sup>, A. SMELLEY<sup>1</sup>, G. CHELLIAH<sup>1</sup>, D. A. NARVAIZ<sup>5</sup>, L. BURGE<sup>1</sup>, C. LAU<sup>3</sup>, K. LALLY<sup>1</sup>, L. DOUGLAS<sup>1</sup>, J. N. LUGO, Jr.<sup>4</sup>;

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**Abstract: Background** Epilepsy is a neurological disorder characterized by abnormal electrical activity in the brain, which is prevalent during childhood, and increases the risk of developing cognitive and behavioral comorbidities. Seizures can influence the release of cytokines, which increases excitability and the likelihood of additional seizures. Dysregulations in the mechanistic target of rapamycin (mTOR) pathway have been found in epilepsy syndromes and disorders associated with autism spectrum disorder. Rapamycin is an inhibitor of mTOR protein kinase, while minocycline is an anti-inflammatory drug, and both are effective in treating epilepsy. The present study examined the role of PI3k/Akt/mTOR pathway activity and neuroinflammation in the development of autistic-like behaviors following seizures in the neonatal period. **Methods** We used C57BL/6J mice to investigate the role of neonatal seizures in the development of autistic-like behaviors. Seizures were induced on postnatal day (PD) 10 via an injection of 0.5% kainic acid. Three hours later, we treated the mice with either saline (S), minocycline (M), rapamycin (R), or both minocycline and rapamycin (M/R). Finally, at two months, we ran the mice through a battery of behavioral assays. **Results** Analysis of the data from open field and elevated plus maze shows that seizures did not influence locomotor activity or anxiety behaviors. However, the R and M/R treatment group traveled a significantly shorter total distance and distance in the center and surround areas than the M and S groups in the open field. The R group went into the closed arms less frequently than the S groups in the elevated plus maze. M/R mice had more repeated nose pokes than S mice and in the marble burying task, seizures resulted in a decrease in marbles buried compared to controls. Treatment with R and M/R caused a decrease in cup and chamber frequency compared to S and M groups in the social chamber task. Seizures resulted in an increase in freezing behavior in both context and tone conditions in delay fear conditioning. Treatment with R and M/R also caused an increase in freezing behavior for context alone. **Discussion** We found that the mice treated with R and M/R had decreased activity. We did not see an effect of seizures or treatment on repetitive behaviors or anxiety-like behaviors. We saw that both seizures and treatment with R and M/R increased fear memory in the delay fear conditioning tasks. Overall, we believe our results will be able to give a more comprehensive view of the developmental profile of early-life seizures and autistic like behaviors, and the beneficial effects of rapamycin and minocycline.

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**Poster**

**PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.07/A47

**Topic:** A.06. Developmental Disorders

**Support:** R35NS127253  
R37NS033123  
R21 NS104799

**Title:** Presymptomatic gene expression profiling of cerebellum in the Shaker rat, a model of Christianson syndrome

**Authors:** \*P. HIVARE<sup>1</sup>, K. FIGUEROA<sup>1</sup>, D. R. SCOLES<sup>1</sup>, S. M. PULST<sup>2</sup>;  
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**Abstract:** Christianson Syndrome (CS) is a rare X-linked neurodevelopmental disorder caused by loss-of-function mutations in the *SLC9A6* gene. CS leads to intellectual disability, autism-like behaviors, epilepsy, and ataxia. Understanding the molecular mechanisms that underlie CS is essential for developing effective therapeutic strategies. We recently showed that the *Shaker* rat with ataxia, tremor, and Purkinje cell degeneration has an indel mutation in *Slc9a6*. This makes it a valuable model for studying CS, especially cerebellar dysfunction. This study aimed to elucidate temporal changes and direct differences in gene expression during early development in wild-type (WT) and affected *Shaker* rats to identify key pathways involved in disease progression. We conducted bulk RNA sequencing using cerebellar tissue from WT and *Shaker* at 1 and 3 weeks of age. Differential expression analysis, Gene Ontology enrichment analysis, and Gene Set Enrichment Analysis were used to identify significantly altered biological pathways. Overall, there were >5,000 differentially expressed upregulated and downregulated genes (DEGs) between wildtype and *Shaker* at the 2 time points. Gene analysis for *Shaker* vs. WT at 1 week showed significant enrichment in nervous system development and synaptic transmission, indicating early disruptions in neuronal maturation and function similar to those observed in human CS. At 3 weeks, activation of the neuroactive ligand-receptor interaction pathway indicated persistent alterations in neurotransmission that may contribute to progressive cerebellar atrophy. In WT rats from 1 to 3 weeks, gene analysis revealed significant enrichment in immune activation pathways and downregulation of cell cycle processes, reflecting normal cerebellar maturation. In *Shaker* from 1 to 3 weeks, there was enrichment in GABAergic synaptic transmission and downregulation of neuron differentiation pathways. These suggest impaired neuronal maturation and connectivity, potentially contributing to cognitive deficits, and progressive ataxia observed in human CS. Our findings demonstrate distinct developmental gene expression patterns in WT and *Shaker* rats at very early time points and 10 weeks prior to ataxia onset. The dysregulation of GABAergic transmission and neuronal differentiation in *Shaker* rats may contribute to the neurological phenotypes observed in CS. Our data indicate that transcriptomic changes in *Shaker* are evident 10-12 weeks before symptom onset and highlight the potential need for early therapeutic intervention in CS to mitigate disease progression.

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**Poster**

**PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR201.08/A48

**Topic:** A.06. Developmental Disorders

**Title:** Phosphoprotein enriched in astrocytes-15 KDa (PEA15) in neurodevelopment: integrating phenotype and transcriptomic analyses in domestic cats

**Authors:** \*S. SALIMIYAN<sup>1,3</sup>, T. TOWNS<sup>1,3</sup>, R. WATANABE<sup>1,3</sup>, E. J. BRINKER<sup>4</sup>, A. B. YANKE<sup>5</sup>, A. BASHIR<sup>6,7</sup>, O. GRIGSBY<sup>1,3</sup>, A. GROSS<sup>3</sup>, D. R. MARTIN<sup>3,2</sup>, E. C. GRAFF<sup>1,3</sup>;  
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**Abstract:** Neurodevelopmental disorders are part of a broad spectrum of neurologic disease including autism, intellectual deficits, and movement disorders. Phosphoprotein enriched in astrocytes-15kDa (PEA15) is an intracytosolic regulator of key neurodevelopmental processes including glucose uptake. Recently, our lab identified a loss of function mutation in PEA15 in domestic cats that results in microcephaly and polymicrogyria; however, little is known about the role of PEA15 in normal neurodevelopment. The objectives of this study are 1) further characterize the clinical aspects including developmental milestones, neuroanatomical changes, and clinicopathologic and neurological exam findings in cats with PEA15 loss of function, and 2) explore potential mechanisms through transcriptomic analysis of the cerebral cortex of adult (>1 year) and developing (<4 months) affected cats and age-matched controls. On MRI, affected cats had smoothing of the cerebral cortex with reduced gyral formation, and overall loss of white matter. Affected kittens had minimal developmental delays with only delayed claw retraction noted at 3 weeks old. On neurologic exam, at 2 months, affected cats consistently showed delayed knuckling and spastic withdrawal reflexes. Menace response was absent in affected adult cats, and there was potential decreased vision tracking. By 6 months of age, affected cats had significantly shorter front and rear stride length and kittens had a hypermetric, ataxic gait with decreased forward progress. Differential gene expression analysis of the cerebral cortex identified overexpression of genes involved in glucose metabolism, axon elongation, and synaptic plasticity. Network analysis indicated disruption of pathways related to energy metabolism and cellular growth. Interestingly, affected cats lacked significant changes in systemic or cerebrospinal fluid glucose biomarkers of energy metabolism. These findings underscore the critical role of PEA15 in neurodevelopment and neurometabolism. Further studies are needed to explore molecular mechanisms.

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**Poster**

## **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.09/A49

**Topic:** A.06. Developmental Disorders

**Support:** NIH Grant P50MH106438  
Burroughs Wellcome Fund Next Generation Pregnancy Initiative

**Title:** Epigenetic signatures of maternal immune activation in brain regions governing social and cognitive function

**Authors:** \*F. J. CARBAJAL<sup>1</sup>, J. HUBBARD<sup>1</sup>, V. HAGHANI<sup>1</sup>, E. CARLSON<sup>2</sup>, S. MONTERO-DE LA TORRE<sup>1</sup>, C. PHI<sup>1</sup>, A. M. RYAN<sup>5</sup>, A.-M. IOSIF<sup>1</sup>, S. CHEN<sup>1</sup>, D. YASUI<sup>1</sup>, C. M. SCHUMANN<sup>2</sup>, E. L. KINNALLY<sup>3</sup>, J. LASALLE<sup>6</sup>, M. D. BAUMAN<sup>4</sup>;

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**Abstract:** Early infection during pregnancy is implicated in the onset of offspring neurodevelopmental disorders (NDDs). Rodent maternal immune activation (MIA) models suggest that the risk is not tied to underlying viral or bacterial strains; instead, maternal cytokine exposure during pregnancy is sufficient to induce NDD-like phenotypes. However, rodent MIA models have limitations for further investigation; nonhuman primates offer greater translational relevance due to their closer evolutionary relationship to humans. Pregnant rhesus macaques (*Macaca mulatta*) were inoculated with the viral mimic Poly(I:C) during the late first trimester to induce a transient immune response. Male offspring (N = 12 MIA, 14 Control) were assessed on the visual paired comparison (VPC) task at 3 months of age, and on the social interest (SI) task at 11, 23, and 35 months. Infant MIA-exposed offspring spent more time looking at novel stimuli than controls during the VPC task. During the SI task, juvenile MIA-exposed offspring spent more time in proximity to a novel conspecific than controls at 11 months of age and spent more time in the social chamber overall. However, this effect was no longer significant at 23 or 35 months. These behavioral alterations suggest possible neurodevelopmental disruption in the dorsal lateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (DACC), regions implicated in executive functioning and emotion regulation, respectively. To investigate potential mechanisms underlying these behavioral differences in the DLPFC and DACC, we are currently analyzing whole genome bisulfite sequencing (WGBS) data from both regions to identify differentially methylated regions (DMRs) and correlated methylation gene networks that will be correlated with VPC data at the individual animal level. These DNA methylation signatures can provide insight into the gene pathways contributing to atypical social behavior and potentially provide predictive perinatal biomarkers in humans. Analysis of methylation patterns is ongoing, and we anticipate that MIA-exposed offspring will exhibit DNA methylation changes in neurodevelopmentally relevant genes.



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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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**Topic:** A.06. Developmental Disorders

**Support:** Foundation for Prader–Willi Syndrome Research Grant 22-0321 and 23-0447 (to K.F.T and Z.K.)  
Cancer Prevention and Research Institute of Texas Scholar Award RR200059 (to K.F.T.).  
Texas Tech University start-up (to K.F.T.)

**Title:** Loss of the Prader-Willi Syndrome gene *MAGEL2* rewires mRNA translation in the mouse hypothalamic and pituitary neuroendocrine systems

**Authors:** \*T. BAYAT<sup>1</sup>, M. HOYOS SANCHEZ<sup>2</sup>, C. RODRIGUEZ ALMONACID<sup>3</sup>, E. TIKHONOVA<sup>3</sup>, J. SOLANO<sup>4</sup>, F. POPY<sup>2</sup>, S. MYERS<sup>2</sup>, A. KARAMYSHEV<sup>3</sup>, Z. KARAMYSHEVA<sup>3</sup>, K. FON TACER<sup>1</sup>;

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**Abstract:** Control of mRNA translation is a crucial regulatory mechanism in neural gene expression, particularly in the hypothalamic neuroendocrine neurons that require high rates of protein synthesis for hormone production. Dysregulation of translational homeostasis is recognized in neurodevelopmental diseases, yet its contribution to Prader-Willi Syndrome (PWS) remains unexplored. PWS is a neurodevelopmental disorder characterized by dysfunction of the hypothalamic neuroendocrine system and hypothalamic-pituitary-adrenal axis (HPA). PWS results from the loss of several imprinted genes, including melanoma antigen L2 (*MAGEL2*), which has been implicated in the regulated secretion by hypothalamic neurons. We hypothesized that *MAGEL2* also regulates mRNA translation in hypothalamic neuroendocrine circuits. To investigate the potential role of *MAGEL2* in neural mRNA translation, we performed polysome profiling on the hypothalamus and pituitary gland from 16 wild-type and *Magel2*<sup>pΔ/m+</sup> mice. Following sucrose gradient ultracentrifugation, mRNAs associated with varying numbers of ribosomes, including monosomes, light polysomes, and heavy polysomes were separated, which reflect translation efficiency from low to high, respectively. RNA from each group of fractions was subjected to RNA sequencing and differential expression analysis. Loss of *MAGEL2* resulted in significant alterations in the translome of both the hypothalamus and pituitary. We identified 650, 746, and 436 differentially translated transcripts in the monosome,

light polysome, and heavy polysome fractions of the pituitary, respectively. In the hypothalamus, we detected 1991, 2293, and 1562 differentially translated transcripts in the corresponding fractions. Interestingly, mRNAs of several translation factors, ribosomal proteins, and hormones, including prolactin, as well as ion channels and synaptic factors, were differentially translated. These findings underscore a critical role for MAGEL2 in maintaining mRNA translational balance in the neuroendocrine circuits and suggest that its loss may underlie neuroendocrine dysfunction observed in PWS. Together, our data provide novel insight into the role of MAGEL2 in regulation of neuroendocrine function with implications for therapeutic interventions in patients with PWS and related syndromes.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.11/A51

**Topic:** A.06. Developmental Disorders

**Support:** NIH Grant ES35851  
NIH Grant GM139753

**Title:** Methylmercury's impact on redox homeostasis and parvalbumin-expressing interneuron maturation

**Authors:** \*M. WATANABE<sup>1</sup>, K. ROSHTO<sup>2</sup>, A. SASUCLARK<sup>3</sup>, M. W. PITTS<sup>4</sup>;  
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**Abstract:** Methylmercury (MeHg) is an environmental neurotoxin found in marine food chains, and it has been shown to severely impact the developing brain. Whereas the neurotoxic effects of MeHg are well established, the underlying mechanism still requires clarification. Evidence suggests that MeHg targets thiol and selenol groups that play critical roles within antioxidant systems. Selenium (Se) is an essential trace element ingested through the diet and incorporated into selenoproteins as the catalytic amino acid selenocysteine (Sec). Optimal levels of Se are crucial for maximizing the activity of redox-regulating selenoproteins such as glutathione peroxidase (GPX) and thioredoxin reductase (TXNRD), which are vital for maintaining brain health. There is evidence that MeHg induces conditions reminiscent of Se deficiency *in vitro*, and studies in rodents have shown that additional Se supplementation can mitigate MeHg toxicity. Parvalbumin Interneurons (PVIs), a subtype of GABAergic interneuron that expresses the calcium-binding protein Parvalbumin, are increasingly vulnerable to oxidative damage due to

their high metabolic activity. PVIs are vital for the maintenance of proper excitatory/inhibitory tone in neural networks and the modulation of gamma oscillations. During development, PVIs are preferentially surrounded by Perineuronal Nets (PNNs), extracellular matrix structures that protect PVIs from oxidative insults and stabilize synaptic connections. Elevated levels of ROS during adolescence have been shown to impair PVI and PNN development *in vivo*, leading to lasting alterations in excitatory/inhibitory balance. Furthermore, abnormalities in PVIs and PNNs are well documented in neuropsychiatric disorders. In this study, we examined the interactive effects of Se and MeHg on PVI and PNN maturation *in vitro*. Mixed primary cortical cultures were raised in Se optimal media (100 nM Se) until DIV14 (days in vitro), after which they were challenged with a subtoxic dose of MeHg (200 nM) from DIV14-DIV28, a critical period when cortical networks and PNNs stabilize. At DIV28, MeHg treatment impaired antioxidant defense, as activity of thioredoxin and thioredoxin reductase were significantly decreased. Electrophysiological analysis using microelectrode arrays (MEA) further revealed that MeHg treatment disrupted neural network connectivity and impaired synaptic plasticity. Moreover, administration of additional Se (400 nM) from DIV14-DIV28 mitigated many of these effects, demonstrating a protective role against MeHg. Altogether, these results demonstrate the interactive effects of Se and MeHg on redox homeostasis and GABAergic maturation.

**Disclosures:** M. Watanabe: None. K. Roshto: None. A. Sasuclark: None. M.W. Pitts: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.12/A52

**Topic:** A.06. Developmental Disorders

**Title:** Reelin haploinsufficiency contributes to the pathophysiology of Autosomal Dominant Lateral Temporal Epilepsy

**Authors:** \*C. BAO<sup>1,2</sup>, G. DILLON<sup>2</sup>, U. BEFFERT<sup>1</sup>, A. HO<sup>1</sup>;

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**Abstract:** Autosomal dominant lateral temporal epilepsy (ADLTE) is a rare neurological disorder characterized by focal seizures, auditory auras, and aphasic symptoms. Approximately 20% of familial ADLTE cases are caused by heterozygous missense variants in the *RELN* gene. *RELN* encodes Reelin, a large secreted glycoprotein essential for cortical lamination during development and synaptic plasticity in the adult brain. Despite this genetic link, the pathogenic mechanisms by which *RELN* variants lead to epilepsy remain poorly understood. We aim to elucidate the cellular and molecular mechanisms underpinning Reelin's role in ADLTE and to evaluate the potential of CRISPR activation (CRISPRa) as a targeted therapeutic approach for ADLTE. To date, eight heterozygous *RELN* missense variants have been identified. We examined their impact on the Reelin signaling pathway by assessing Reelin secretion, extracellular cleavage, receptor binding, and downstream signaling. Seven of the eight variants

resulted in markedly reduced Reelin secretion, leading to intracellular accumulation of unsecreted protein. Immunoblot analysis confirmed that none of the variants affected Reelin cleavage. In addition, all *RELN* variants retained the ability to bind its receptor ApoER2 in HEK293T cells and to activate downstream Dab1 phosphorylation in human iPSC-derived neurons. Co-transfection experiments further showed that the variants do not exert dominant-negative effects on wild-type Reelin secretion in HEK293T cells. These findings suggest that impaired secretion is the predominant defect caused by pathogenic variants in ADLTE, consistent with a loss-of-function mechanism due to Reelin haploinsufficiency. The large size of the *RELN* coding sequence poses a significant challenge for conventional gene replacement or protein delivery approaches to correct Reelin haploinsufficiency. To explore an alternative strategy, we tested whether CRISPR activation could be used to upregulate endogenous Reelin expression. We employed a dCas9-based transcriptional activator system (dCas9-VPH), which incorporates VP64, p65, and HSF1, together with guide RNAs targeting the *RELN* promoter in HEK293T cells. Our results show that the dCas9-VPH system significantly increases both *RELN* transcript and Reelin protein levels. These findings support the potential of CRISPRa-mediated gene activation as a viable therapeutic approach for ADLTE caused by *RELN* haploinsufficiency.

**Disclosures:** C. Bao: None. G. Dillon: None. U. Beffert: None. A. Ho: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.13/A53

**Topic:** A.06. Developmental Disorders

**Support:** NIH Grant EPEX80027  
EMUNV 7250000496  
Marcus J Zhou Start-Up 7365380212

**Title:** A tale of two mutations: how phf14 loss and gain variants disrupt brain development

**Authors:** \*Y. WU;  
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**Abstract:** Plant Homeodomain Finger Protein 14 (PHF14) is an epigenetic regulator with critical roles in cell proliferation and differentiation, cancer, fibrosis, and neurodevelopmental disorders (NDDs). As a chromatin-associated protein, PHF14 modulates gene expression by interacting with TCF20 and MeCP2—the causal genes for Rett Syndrome (RTT) and TCF20 associated NDD, respectively—within the TCF20/PHF14 complex. We previously identified a *PHF14* missense variant (c.964T>G, p.C322G) in an NDD patient presented with clumsy gait, developmental delay/intellectual disability, speech delay, and an RTT-like regression in gross motor skills and balance. This mutation disrupts the interaction between PHF14, TCF20, and MeCP2 within the complex. Our clinical and biochemical findings highlight the strong link

between TCF20/PHF14 complex and NDD pathogenesis; however, the underlying neuronal and molecular mechanisms remain unclear. To understand the role of PHF14 in brain development, we generated *Phf14* knockout (KO) and *Phf14*-C322G knock-in mouse models, collected the brain tissues at various developmental stages to assess the impact of PHF14 mutations on neurodevelopment by employing Western blot, immunostaining, Co-IP, and RNA-seq analyses. At the early stage, *Phf14* deletion impairs cortical development by reducing SOX2 expression and decreasing the number of PHH3<sup>+</sup> and Satb1/2<sup>+</sup> cells at E17.5, suggesting that PHF14 plays an important role in regulating the mitotic activity, proliferation, and differentiation of neural progenitor cells. RNA-seq analysis reveals disrupted neurodevelopmental pathways, including neuropeptide signaling, cell-cell signaling, and neurogenesis in *Phf14* KO mice. Furthermore, *Phf14* KO mice exhibit neonatal lethality at P0, highlighting its essential role in development. Notably, homozygous *Phf14*<sup>C322G/C322G</sup> mice exhibit an earlier embryonic lethality at E15.5, whereas heterozygous *Phf14*<sup>-/C322G</sup> mice remained viable into adulthood, suggesting that the C322G mutation is a potential gain-of-function variant by enhancing ectopic PHF14 functions rather than causing a complete loss of function. Our study established PHF14 as a key regulator in brain development and reveals novel molecular mechanisms underlying both loss- and gain-of-function effects of PHF14 mutations, shedding light on its role in NDD pathogenesis.

**Disclosures:** Y. Wu: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.14/A54

**Topic:** A.06. Developmental Disorders

**Support:** DOD W81XWH-19-1-0402

**Title:** Characterization of cortical development in mouse models of neurofibromatosis type-1 and elevated ERK/MAPK Activity

**Authors:** \*B. REES<sup>1</sup>, L. XING<sup>2</sup>, M. J. ZYLKA<sup>3</sup>;

<sup>1</sup>Perelman Sch. of Med., Univ. of Pennsylvania, Philadelphia, PA; <sup>2</sup>Univ. of North Carolina, Chapel Hill, NC; <sup>3</sup>Dept Cell & Mol Physiol, Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

**Abstract:** Neurofibromatosis type-1 (NF-1) is a common neurodevelopmental disorder characterized by a range of symptoms, including neurofibromas and cognitive deficits. Neurofibromin (NF1), the protein expressed by the *NFI* gene, is an important regulator in the Ras signaling pathway, and the precise mechanisms by which NF1 deficiency leads to the pathogenesis of the NF-1 cognitive phenotype are not well understood. The present study aims to address this knowledge gap by investigating the effects of NF1 deficiency on cortical neuron and oligodendrocyte development, exploring both the impact of decreased *NFI* expression and

isolated upregulation of downstream signaling pathways on cortical development. We used a combination of *Nf1* conditional knockout (cKO) mouse models and mouse models exhibiting ERK/MAPK hyperactivity—a critical signaling pathway downstream of Ras—to model the biochemical expression of NF-1, and immunolabeling for layer-specific neurons and oligodendrocytes at different developmental stages was used to quantify changes in cortical development. In our NF1-deficient model, we identified both a significant reduction of upper layer excitatory neuron number and an overproduction of oligodendrocyte progenitor cells (OPCs) within the cortex. However, despite identifying a similar reduction of upper layer excitatory neuron number in our hyperactive ERK/MAPK model, we observed only a slight increase in OPC density as compared to the *Nf1* cKO models. To explore how the developmental trajectory of neurons and oligodendrocytes is affected by decreased NF1 production and the resulting upregulation of the ERK/MAPK signaling pathway, we performed EdU pulse labeling, ultimately identifying signs of precocious neurogenesis and gliogenesis in both models. Collectively, these results further characterize the effects and mechanisms by which decreased NF1 production affects cortical development.

**Disclosures:** B. Rees: None. L. Xing: None. M.J. Zylka: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.15/A55

**Topic:** A.06. Developmental Disorders

**Title:** The schizophrenia-associated 3q29 deletion: at the intersection of mitochondrial dysregulation, E/I imbalance, and altered circuit dynamics

**Authors:** \*M. S. SCARNATI, R. POLLAK, R. SEBASTIAN, J. G. MULLE;  
Rutgers, The State Univ. of New Jersey, Piscataway, NJ

**Abstract:** Schizophrenia (SZ) is a severe, chronic psychiatric disorder that impacts up to 1% of the population. Despite extensive research, its extreme heterogeneity has posed a major challenge to understanding its underlying mechanisms. Cellular and animal models of SZ demonstrate metabolic dysregulation, including impaired mitochondrial function, and altered energy metabolism. Hippocampal hyperexcitability, particularly in CA1, has also been hypothesized to contribute to schizophrenia risk, possibly due to disrupted inhibitory-excitatory balance contributing to aberrant circuit activity. These two factors may intersect during early postnatal brain development, where deficits in bioenergetics lay the groundwork for disrupted neuronal metabolism or synaptic signaling, potentially contributing to the increased incidence of developmental and behavioral deficits observed in affected individuals. We *hypothesize* that impaired mitochondrial energy production compromises inhibitory interneuron function, thereby promoting network hyperexcitability and contributing to the pathophysiology of SZ. To test this, we will use the SZ-associated 3q29 deletion, a well-defined genetic model of SZ. This rare

variant increases the risk of SZ by 40-fold, the highest effect size of any SZ risk factor. Using Seahorse respirometry we observe metabolic dysregulation in cells harboring the 3q29 deletion, including reduced mitochondrial flexibility ( $p=0.0006$ ), impaired glycolysis ( $p=0.01$ ), and an increased reliance on fatty acids as substrates for electron transport ( $p=0.05$ ). To assess whether metabolic flexibility correlates with patient phenotypes, we calculated mitochondrial health indices as a potential predictor of phenotype severity from patient derived iPSC lines. Finally, patch-clamp electrophysiology was used to measure the passive and spontaneous properties of CA1 pyramidal cells isolated from the syntenic 3q29 mouse model. We observe a significant increase in CA1 Ih currents ( $p=0.01$ ), indicating altered HCN channel function in 3q29Del animals. Moreover, the output of CA1 pyramidal cells was measured as a function of the synaptic inputs they receive following stimulation of Shaffer collaterals. Future work will focus on testing drugs that modulate mitochondrial function to determine whether they can rescue physiological deficits associated with the 3q29 deletion. These studies aim to identify therapeutic strategies that restore cellular metabolism and improve disease-related outcomes. Our overall goal is to understand, mechanistically, if metabolic dysregulation is a cause or an effect of neurodevelopment anomalies associated with SZ.

**Disclosures:** M.S. Scarnati: None. R. Pollak: None. R. Sebastian: None. J.G. Mulle: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.16/A56

**Topic:** A.06. Developmental Disorders

**Support:** NIH NINDS R01 NS125778

**Title:** Neurodevelopmental consequences of ZIKV vertical transmission: Peli1-dependent neural stem cell loss

**Authors:** \*K. TRINH<sup>1</sup>, J. TIERNEY<sup>2</sup>, P. WU<sup>3</sup>;

<sup>1</sup>Neurobio., Univ. of Texas Med. Br. at Galveston, Galveston, TX; <sup>2</sup>Univ. of Texas Med. Br. at Galveston, GALVESTON, TX; <sup>3</sup>Univ. of Texas Med. Br., Galveston, TX

**Abstract:** Zika virus (ZIKV) infection during pregnancy causes congenital Zika syndrome (CZS), which includes microcephaly and other neurodevelopmental consequences. While ZIKV can infect neural progenitor cells (NPCs), the low infection rate doesn't explain the damage observed in the embryonic brain. Microglia—the yolk sac-derived immune cells that regulate neurodevelopment—have emerged as potential mediators of ZIKV-induced pathology. Peli1, an E3 ubiquitin ligase enriched in microglia, regulates innate immune responses and may influence how microglia respond to viral infection during development. To investigate this, we used Peli1 knockout (PKO) mice in a vertical transmission model of ZIKV. Pregnant wild-type (WT) and PKO dams were infected mid-gestation, and embryonic brains were analyzed by

immunohistochemistry for Sox2 and Ki67 to quantify neural stem cell (NSC) populations and proliferation. ZIKV infection trended toward a reduction in Sox2<sup>+</sup> cell numbers in WT embryos, consistent with NSC depletion and impaired neurogenesis. Comparatively, PKO embryos showed higher levels of Sox2<sup>+</sup> cells and less severe morphological abnormalities, suggesting attenuation. In parallel, immunohistochemistry of yolk sac tissue revealed that ZIKV reduced the number of F4/80<sup>+</sup> yolk sac macrophages, an effect attenuated in PKO embryos, suggesting Peli1 contributes to depletion or dysregulation of early microglial progenitors. Despite ZIKV infection, proinflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$  were not upregulated in the embryonic brain, suggesting non-inflammatory mechanisms of microglial-mediated neurodevelopmental disruption. These findings support a model in which Peli1 contributes to ZIKV-induced neurodevelopmental damage by modulating microglial function. Ongoing studies look at how ZIKV-infected microglia influence neural stem cell dynamics and contribute to neurodevelopmental disruption. Together, our results implicate Peli1-dependent microglial signaling in ZIKV pathogenesis and that targeting this pathway may protect the developing brain. This work provides new insight into how non-neuronal cells contribute to congenital viral syndromes and identifies Peli1 as a potential therapeutic target.

**Disclosures:** K. Trinh: None. J. Tierney: None. P. Wu: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.17/A57

**Topic:** A.06. Developmental Disorders

**Support:** NICHD R01 HD042182  
Seale Innovation Fund

**Title:** Targeting oxidative stress rescues cortical projection neuron deficits in a mouse model of 22q11.2 deletion syndrome

**Authors:** \*S. RUKH<sup>1</sup>, D. W. MEECHAN<sup>2</sup>, C. SIGGINS<sup>2</sup>, Z. ERWIN<sup>3</sup>, T. M. MAYNARD<sup>4</sup>, A.-S. LAMANTIA<sup>5</sup>;

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**Abstract:** Layer 2/3 projection neurons (L2/3 PNs) are essential for association cortico-cortical connectivity, and their dysfunction contributes to cortical underconnectivity in neurodevelopmental disorders (NDDs) such as intellectual disability, autism, and schizophrenia. We previously linked oxidative stress and mitochondrial dysfunction to impaired L2/3 PN growth and connectivity in the *LgDel* mouse model of 22q11.2 deletion syndrome (22q11.2DS).



To investigate how 22q11 deletion affects L2/3 PN identity, differentiation, and growth, we integrated in vitro and in vivo approaches, including primary culture assays of L2/3 PN growth, mitochondrial respiration, and multiple transcriptomic analyses. Using primary cortical cultures, we confirmed that the reactive oxygen species (ROS) scavenger N-acetyl cysteine (NAC) significantly improves axonal and dendritic growth in *LgDel* L2/3 PNs. However, RNA sequencing showed that NAC did not restore expression of heterozygously deleted 22q11 genes or normalize expression of wild-type (WT) vs. *LgDel* differentially expressed (DE) genes. Instead, NAC induced robust changes in a distinct DE gene set, enriching antioxidant pathways—particularly the Nrf2 signaling cascade. These changes were validated via qPCR and spatial transcriptomics, confirming novel NAC-mediated DE gene expression without upregulation of 22q11 or WT vs. *LgDel* genes. Mitochondrial respiration assays revealed bioenergetic deficits in *LgDel* L2/3 PNs, partially rescued by NAC. We are validating and extending these observations using high-resolution single-cell spatial transcriptomics of postnatal day 6 *LgDel* and WT cortex to better resolve L2/3 PN identity, layer-specific oxidative stress signatures and antioxidant gene response after NAC treatment. Together, our findings demonstrate that 22q11 deletion results in transcriptional, bioenergetic, and developmental disruptions in L2/3 PNs. Accordingly, oxidative stress may be a key modifiable driver of suboptimal cortical connectivity. These results highlight a potential therapeutic avenue that operates independently of 22q11 gene rescue, by supplementing mitochondrial antioxidant defense to support the energetic demands of developing L2/3 PNs.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.18/A58

**Topic:** A.06. Developmental Disorders

**Support:** The National Institutes of Health (NIH)

**Title:** Do Kismet and CREB Binding Protein (CBP) cooperatively promote synaptic functions?

**Authors:** \*N. ASSI, F. L. LIEBL;

Dept. of Biol. Sci., Southern Illinois Univ. Edwardsville, Edwardsville, IL

**Abstract:** Synaptic dysfunction is a hallmark of neurodevelopmental disorders and neurodegenerative diseases including Alzheimer's disease (AD), CHARGE syndrome, and autism spectrum disorders. Epigenetic mechanisms including chromatin remodeling and histone modification play a critical role in the development and maintenance of synaptic functions. Although there is some understanding of the role of chromatin remodeling proteins in promoting synaptic functions, how they interact with histone-modifying enzymes to orchestrate the

transcription of genes essential for synaptic function remains largely unresolved. This study explores the potential cooperative function of Kismet, a *Drosophila* ortholog of the human chromatin remodeling enzymes CHD7 and CHD8, and CREB-binding protein (CBP), a histone acetyltransferase, in regulating histone modifications associated with active chromatin states. In contrast, components of Polycomb Repressive Complexes 1 and 2 (PRC1 and PRC2) act in opposition to Kismet, promoting repressive chromatin states. We found that global levels of histone H3 lysine 27 acetylation (H3K27ac) and trimethylation (H3K27me3) in the ventral nerve cord (VNC) of larval *Drosophila melanogaster* models with haploinsufficiency in key epigenetic regulators, as well as in an AD-associated fly model, showed no significant changes. Global levels of H3K27ac and H3K27me3 in the VNC remained consistent across all genotypes. We will next investigate the functional relationship between Kismet, CBP, PRC1, and PRC2 in regulating gene expression of targets coding for synaptic proteins including Amyloid Precursor Protein Like (APPL), Fasciclin II, Rab11 and Endophilin B. While aberrant synaptic functions in neurodevelopmental disorders and neurodegenerative diseases may not involve global alterations in H3K27, it may involve alterations of specific synaptic proteins.

**Disclosures:** N. Assi: None. F.L. Liebl: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.19/A59

**Topic:** A.06. Developmental Disorders

**Support:** NSF Graduate Research Fellowships Program  
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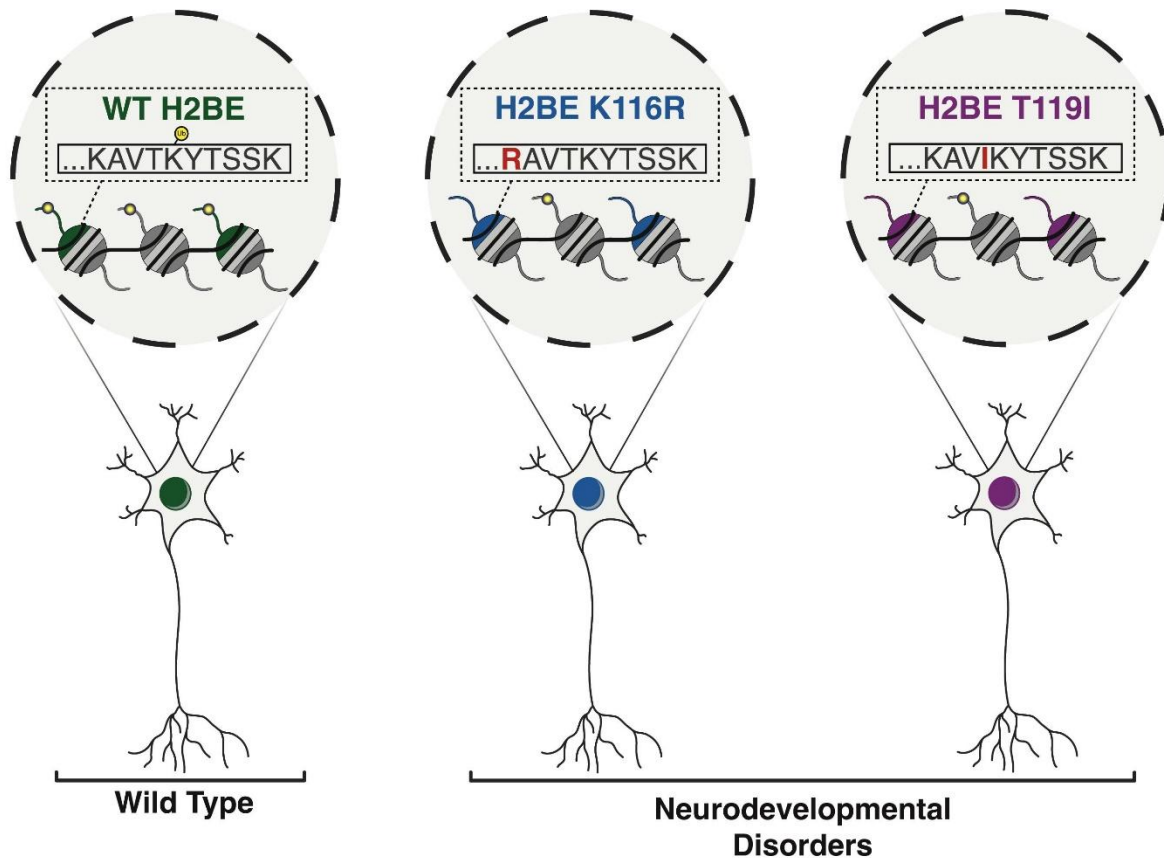
**Title:** Elucidating the roles of histone variant H2BE (H2BC21) in human neurodevelopment

**Authors:** \*A. J. VOSS<sup>1</sup>, E. HYATT<sup>2</sup>, E. KORB<sup>2</sup>;

<sup>1</sup>Neurosci. Grad. Group, <sup>2</sup>Genet., Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Histone variants replace canonical histones and are encoded by unique genes with distinct sequences from their canonical counterparts. Recently, the importance of histone variants in neurodevelopment has become increasingly appreciated with variants such as H3.3 and H2A.Z linked directly to neuronal function and neurodevelopmental disorders. However, the roles of H2B variants in neurodevelopment are poorly understood. H2BE, encoded by *H2BC21*, is the sole variant of H2B known to be expressed outside of germline tissues. Our lab discovered that H2BE is broadly expressed throughout the brain and is highly localized to promoters. Further, we found that loss of H2BE leads to decreases in chromatin accessibility throughout the genome,

changes in neuronal gene expression, and deficits in long-term memory. In collaboration with clinicians, we identified multiple *de novo* *H2BC21* putative germline variants (PGVs) in patients presenting with developmental delays, intellectual disability, short stature, and microcephaly. Utilizing biochemical approaches, CUT&Tag, and ATAC-sequencing, we aim to elucidate how *H2BC21* PGVs affect H2BE incorporation, localization within the genome, and chromatin accessibility in human embryonic stem cell-derived neural progenitor cells and neurons. This study is the first to directly implicate a H2B variant histone in neurodevelopmental disorders and is critical to our understanding of how H2BE, and histone variants broadly, alter chromatin regulation and function in the brain.



**Disclosures:** A.J. Voss: None. E. Hyatt: None. E. Korb: None.

**Poster**

**PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.20/A60

**Topic:** A.06. Developmental Disorders

**Title:** Structural cytogenetic and phenotypic profile of Brazilian families with 9p chromosomal alterations.

**Authors:** \*I. M. VAZ<sup>1,2</sup>, M. M. OLIVEIRA<sup>2</sup>, I. N. MASSON<sup>2</sup>, N. E. TRENTINY<sup>2</sup>, M. M. A. FUGIMOTO<sup>4</sup>, V. N. S. HABE<sup>4</sup>, C. L. K. REBELATTO<sup>5</sup>, P. S. BROFMAN<sup>3</sup>, R. H. HERAI<sup>2,6</sup>; <sup>2</sup>Hlth. Sci. Grad. Program, Multiuser Exptl. Lab. (LEM), Lab. of Bioinformat, <sup>3</sup>Sch. of Med. and Life Sciences, Core Cell Technol., <sup>1</sup>Pontificia Univ. Católica do Paraná, Curitiba, Brazil; <sup>4</sup>9p Brazil Assn., Santa Maria, Brazil; <sup>5</sup>Sch. of Med. and Life Sciences, Core Cell Technol., Pontificia Univ. Católica do Paraná, Curitiba, Brazil; <sup>6</sup>Res. Div., Buko Kaesemodel Inst. (IBK), Curitiba, Brazil

**Abstract:** Introduction: Neurodevelopmental disorders involve a wide spectrum of intellectual disabilities, including autism and other rare forms of syndromes related to short arm 9p chromosome deletion or duplication (SDD9p). SDD9p main symptoms include developmental and social interaction delays, as well as cognitive deficits. Its diagnosis is confirmed by cytogenetic and/or molecular testing to detect alterations in the 9p bands. Currently, only a few works have reported the phenotypes of SDD9p worldwide. Thus, our study is the first to investigate the cytogenetic and clinical phenotypes of SDD9p Brazilian families (including probands and biological parents). Methods: Twenty-two families from all regions of Brazil were interviewed and subjected to intravenous blood collection for karyotyping. The study was approved by the Research Ethics Committee and all study participants signed the Free and Informed Consent Form. Results and Discussion: For all studied families, most probands (n=14; 67%) were female and the average maternal age at birth was 31.6 years. Although 95,5% (n=21) had cognitive deficits, a confirmed diagnosis of autism was found in 47.6% (n=10) of cases. Moreover, all probands have speech delay and hypotonia, difficulty with movement and performing fine motor activities. Furthermore, there are several phenotypes with high variability between probands, with the most prevalent the low-set ears (n=11; 52,3%), followed by dental issues (missing/agenesis of teeth) (n=8; 38%) and trigonocephaly (most underwent surgical procedures during childhood) (n=7; 33%). Regarding cytogenetic analysis, the deletion was the most frequent alteration found (n=15; 68,2%), with the 9p22 and 9p23 bands as the most frequent regions. The second most frequent alteration found was the duplication (n=4; 18,2%). Within the deletion and duplication bands of all probands, it was found an overlapping region at the chromosomal band 9p22.3. In a previous study of Zou et al. (2009), it was associated as a critical region for intellectual development delay in 9p duplication syndrome patients. Conclusions: Our study identified common phenotypic characteristics in 9p probands of a Brazilian population formed by trios. This allowed for a deeper understanding of the clinical patterns characteristic of 9p deletion syndrome, thereby contributing to the broader knowledge of this rare neurodevelopmental condition. By providing novel data for SDD9p biomarker discoveries, we are also addressing an important concern of 9p families in the search for adequate diagnosis and appropriate therapies for this rare syndrome.

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**Poster**

**PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.21/A61

**Topic:** A.06. Developmental Disorders

**Title:** Mutations linked to Nr4a2-related Neurodevelopmental Disorder cause impaired DNA-binding mechanisms, altered gene expression in the hippocampus, and sex-specific memory deficits

**Authors:** \*L. LANGMACK, T. ABEL;  
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**Abstract:** Memory consolidation occurs through transient waves of gene expression in the dorsal hippocampus following a learning experience. The first wave of gene expression peaks within 30-60 minutes, also known as immediate-early genes (IEGs), like Fos, Arc, Nr4a1, and Nr4a2. Nuclear Receptor 4a member 2 (Nr4a2) is a transcription factor that regulates effector gene expression in engram cells of the dorsal hippocampus after spatial learning and contextual fear conditioning. Knockdown of Nr4a2 impairs hippocampal-dependent long-term memory and decreased Nr4a2 expression is linked to neurodegeneration. Mutations in the NR4A2 gene have been linked recently to neurodevelopmental disorders, collectively referred to as Nr4a2-related Neurodevelopmental Disorder (NND) by the Simon's Foundation and National Organization of Rare Diseases. All reported case studies of patients carrying pathogenic mutations in NR4A2 present with developmental delay and Intellectual Disability, and most present with Autism Spectrum Disorder and/or Attention Deficit-Hyperactivity Disorder. This led us to investigate whether certain coding regions of NR4A2 are more susceptible to pathogenic variation and how mutations linked to NND affect the function of the Nr4a2 transcription factor. Using modeling and pathogenicity prediction tools to analyze 500+ patient mutations, we found that mutations in the DNA-binding domain (DBD) are strongly linked to NND diagnoses. Further biochemical studies revealed that missense mutations in the DBD severely impair the transcriptional activity of Nr4a2 as a monomer and dimer, due to lost DNA-binding affinity for its DNA-binding sites in promoter regions. Additionally, DBD mutants change the DNA-binding specificity of Nr4a2 to preferentially bind new regions of the genome, which provides a new model of gene dysregulation by mutant transcription factors. Using a mouse model of Nr4a2 haploinsufficiency, we find that adult male Nr4a2<sup>+/-</sup> mice have memory deficits, but females show fear memory enhancements. Interestingly, both male and female Nr4a2<sup>+/-</sup> mice show increased IEG expression the dorsal hippocampus 1 hour after a learning experience, including genes like Fos, Arc, Egr1, and Nr4a1, that are typically down-regulated in mice with memory deficits. Overall, this study is the first to characterize mutations in *NR4A2* linked to NND and show unique changes in DNA-binding affinity, transcriptional activity, and differential gene expression that impairs memory consolidation.

**Disclosures:** L. Langmack: None. T. Abel: None.

**Poster**

**PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.22/A62

**Topic:** A.06. Developmental Disorders

**Support:** National Research Foundation of Korea [2022R1A2C200341413]  
National Research Foundation of Korea [RS-2024-00344114]  
National Research Foundation of Korea [RS-2025-00513787]

**Title:** Autophagy activation ameliorates SARM1-dependent axon degeneration in CMT2B sensory neuropathy

**Authors:** \*H. KIM, H. PARK;  
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**Abstract: Autophagy activation ameliorates SARM1-dependent axon degeneration in CMT2B sensory neuropathy**

Mutations in Rab7a GTPase (RAB7A) cause the development of hereditary peripheral axonal neuropathy, referred to as Charcot-Marie-Tooth disease 2B (CMT2B). Disturbances in cellular organelle dynamics, such as autophagy, endosomal trafficking, and mitochondrial homeostasis, are related to the pathogenesis of CMT2B. However, the mechanism by which these processes evoke axonal neuropathy in peripheral sensory neurons remains unclear. In this study, we demonstrated that RAB7<sup>L129F</sup> induces axonal degeneration in cultured dorsal root ganglion (DRG) neurons, but the degeneration is mild, not enough to progress to axotomy. In RAB7<sup>L129F</sup>-transduced DRG neurons, mitochondrial oxidative stress was causative of the activation of Sterile alpha and TIR motif-containing protein 1 (SARM1), the critical executor of Wallerian degeneration, and the mitochondrial stress-SARM1 axis induced subsequent mild axon damage. Reversely, dominant negative SARM1 and NAD supplement also prevented mitochondrial dysfunction by RAB7A<sup>L129F</sup>, indicating the feedback mechanism by SARM1 for mitochondrial dysfunction. We observed that RAB7<sup>L129F</sup>-induced autophagy activation precluded the progression of metastable axons to axon degeneration via maintaining axonal NAD<sup>+</sup> and ATP levels. Finally, peripheral sensory neuron-specific transduction of adeno-associated virus of RAB7<sup>L129F</sup> in mice developed abnormal pain sensation with the degeneration of intraepidermal nerve fibers in footpads, and co-transduction of SARM1-dominant-negative mutant blocked axon degeneration and abnormal pain sensation. Our results indicate that mitochondrial stress-SARM1 axis-dependent axonal damages are involved in CMT2B-type axonal neuropathy and that autophagy plays a defensive role in the progression of a metastable axon to severe axonal pathology.

**Disclosures:** H. Kim: None. H. Park: None.

**Poster**

**PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.23/B1

**Topic:** A.06. Developmental Disorders

**Support:** National Science Foundation 2244127  
AACPDM

**Title:** Mechanism of dysregulation of transcription factor MEF2C in spastic cerebral palsy

**Authors:** \***B. M. ROMERO CARPIO**<sup>1</sup>, K. ROBINSON<sup>3</sup>, S. K. YEAGER<sup>3</sup>, V. PARASHAR<sup>2</sup>, R. E. AKINS<sup>4</sup>, M. SHRADER<sup>4</sup>, M. BATISH<sup>2</sup>;

<sup>1</sup>Med. and Mol. Sci., <sup>2</sup>Univ. of Delaware, Newark, DE; <sup>3</sup>Nemours Children's Hlth., Wilmington, DE; <sup>4</sup>Nemours Children's Hlth. Syst., Wilmington, DE

**Abstract:** Spastic cerebral palsy (CP) is the most common motor disability disorder. It is characterized by persistent muscle stiffness and contractures. These musculoskeletal deformities often worsen over time, highlighting the need for timely interventions and therapeutic targets. Myocyte-specific enhancer factor (MEF2C) is a transcription factor that controls muscle development and mediates later differentiation stages in myogenesis. Although MEF2C has been known to regulate the expression of sarcomere genes, it was only recently that our group identified a marked downregulation of MEF2C levels in CP, which could contribute to disrupted sarcomere organization and muscle pathologies reported in CP. We found that under normal development, microRNA 373-3p, which targets MEF2C mRNA, is sponged by a circular RNA called circNFIX, thus allowing MEF2C to be expressed at required levels. In CP, circNFIX is downregulated and thus miR373-3p can target MEF2C RNA and reduce its expression. However, we observed a very marked decrease in MEF2C level despite low copy numbers of miR373-3p, indicating that there might be additional pathways leading to MEF2C regulation. Satellite cell-derived myoblasts (SC-MBs) were isolated from skeletal muscle biopsies from CP (n=9) and control subjects (n=9) under an IRB-approved protocol. The expression of reference markers PAX7 and MYF5 was used to validate the isolated SC-MBs. SC-MBs were cultured and differentiated into myotubes (SC-MTs). RNA-binding proteins (RBPs) interacting with circNFIX were identified using the CRISPR-assisted detection of RNA-protein detection (CARPID). Total RNA was isolated, and qRT-PCR analysis was done to identify RNA expression of the identified RBPs. CircNFIX and RBPs were imaged using single-molecule resolution fluorescence in situ hybridization (smFISH) and immunofluorescence (IFA) to determine copy number, cellular localization, and potential colocalization. A significant reduction in MEF2C levels was found in CP SC-MBs, SC-MTs, and tissues as compared to non-CP controls. smFISH analysis identified increased nuclear localization of circNFIX in CP cells while IF showed reduced MEF2C nuclear expression. CARPID pull down of circNFIX identified TBCE, TBCEA, and additional novel muscle development-associated proteins that could potentially regulate MEF2C expression and/or mediate its function. Interactions between RBPs and circNFIX were shown by smFISH and IF. Future work is aimed at identifying and validating mechanisms of MEF2C regulation so that it can be used as a potential therapeutic target.

**Disclosures:** **B.M. Romero Carpio:** None. **K. Robinson:** None. **S.K. Yeager:** None. **V. Parashar:** None. **R.E. Akins:** None. **M. Shrader:** None. **M. Batish:** None.

## Poster

### PSTR201: Molecular Mechanisms Underlying Developmental Disorders II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.24/B2

**Topic:** A.06. Developmental Disorders

**Support:** NIH Grant 1R21NS142525-01

**Title:** Unraveling the mechanisms of RHOBTB2-related developmental and epileptic encephalopathy

**Authors:** \*A. OLSZEWSKI, H. CHEN, S. PORTER, S. PRUETT-MILLER, H. MEFFORD;  
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**Abstract:** Heterozygous missense variants in the *RHOBTB2* gene are a cause of a developmental and epileptic encephalopathy (RHOBTB2-DEE) characterized by epilepsy, intellectual disability, and motor phenomena. RHOBTB2 is an adaptor protein for CUL3 ubiquitin ligase that assists in selective substrate binding and has been studied in the context of cancer, where its expression is often lost. Understanding the mechanisms of RHOBTB2-DEE will inform the future design of therapeutics and biomarkers for therapy efficacy. Three recurrent variants, R483H, R511W, and R511Q, account for most cases and cause decreased degradation of the RHOBTB2 protein. Individuals haploinsufficient for *RHOBTB2* are healthy, and individuals with biallelic loss-of-function variants have milder phenotypes. We hypothesize that RHOBTB2-DEE variants have a gain-of-function mechanism or mechanism otherwise unique from biallelic loss-of-function. We examined the effect of RHOBTB2-DEE variants on cellular and molecular processes that are impacted by RHOBTB2 loss, including cell proliferation, Hippo pathway signaling, and targets of RHOBTB2-mediated regulation. We used isogenic sets of human induced pluripotent stem cells (iPSCs) and SF126 glioblastoma cell lines with engineered *RHOBTB2* variants (WT, WT/-, WT/R483H, WT/R511Q, WT/R511W). Experiments used two clones per genotype, three wells per clone. In some cancer lines, loss of RHOBTB2 increases cell proliferation. We studied cell cycle using EdU incorporation and DNA staining, followed by flow cytometry analysis. RHOBTB2-DEE variants did not cause a change in cell proliferation of iPSCs. In the Hippo pathway, *RHOBTB2* knockdown causes increased localization of YAP to the nucleus, and subsequent increased expression of Hippo target genes. Immunoblotting showed that iPSC with RHOBTB2-DEE lines had significantly decreased YAP. As measured by RT-qPCR, Hippo pathway targets had significantly lower expression in DEE iPSC lines. MSI2, a protein that is ubiquitinated via interaction with RHOBTB2, has decreased abundance in cells overexpressing WT RHOBTB2 but showed no significant change in abundance in iPSC with RHOBTB2-DEE genotypes. Studies of Hippo signaling showed RHOBTB2-DEE variants have an opposite effect of RHOBTB2 knockdown, while other measures of other cell processes showed no change from RHOBTB2-DEE variants. This may suggest that the DEE variants impact interaction with select substrates, rather than a blanket gain-of-function for all interactions. We are investigating



proteomic and transcriptomic approaches to more efficiently define which proteins have altered degradation in cells with RHOBTB2-DEE.

**Disclosures:** A. Olszewski: None. H. Chen: None. S. Porter: None. S. Pruett-Miller: None. H. Mefford: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.25/B3

**Topic:** A.06. Developmental Disorders

**Title:** Bap1 function in hippocampal development

**Authors:** \*C. LIM<sup>1</sup>, S. KIM<sup>2</sup>;

<sup>1</sup>Lewis Katz Sch. of Med. at Temple Univ., Philadelphia, PA; <sup>2</sup>SHPRC/ACB, Temple Univ. Lewis Katz Sch. of Med., Philadelphia, PA

**Abstract:** As a growing population of patients in the US have been diagnosed with neurodevelopmental disorders, epigenetic causes of these disorders continue to be an active area of study. Prior studies have demonstrated the importance of Bap1, a deubiquitinase enzyme, in many biological functions such as cell cycle, apoptosis, and development. In particular, the Bap1 complex is known to deubiquitinate histone H2AK119, opposing polycomb repressive complex 1 (PRC1) in repressing gene expression through histone modification. A clinical study conducted by Küry et al. describes 11 patients with de novo germline heterozygous missense Bap1 mutations presenting with a variety of NDDs. This suggests that Bap1 has a significant role in brain development, but the function and underlying mechanisms are not yet understood. To investigate the function of Bap1 in brain development, we have generated a conditional knockout mouse lacking Bap1 in the dorsal cortex and hippocampus (Bap1 cKO) using Emx-1 Cre. As such, we hypothesize that Bap1 plays a role in hippocampal progenitor development in the mouse through epigenetic modification and seek to further understand this role through the following overarching aims: (1) to characterize the phenotype of Bap1 cKO in the mouse brain and (2) to determine potential molecular mechanisms of Bap1 function in the mouse hippocampus. Initial behavioral studies of Bap1 cKO mice demonstrate hyperactivity and behaviors associated with autism spectrum disorder as seen in patients with Bap1 neurodevelopmental disorder. Strikingly, we observed developmental defects in the hippocampus that led to significant alterations in the size, shape, and growth of the dentate gyrus (DG). The progenitor population of the DG of Bap1 cKO mice was significantly decreased in neonates followed by dramatic reduction of DG granule cells (DG-GC) and overall size that persists through adulthood. Furthermore, H2AK119Ub concentration was found to be higher in the hippocampus of Bap1 cKO mice, suggesting Bap1 plays a role in epigenetic modification in the hippocampus, and validating the ability of the Bap1 cKO mouse model to mimic the mechanism studied in Bap1 neurodevelopmental disorder. To determine if Bap1 loss results in

alterations in gene expression and chromatin accessibility, single cell nuclei gene expression profiling and ATAC seq was conducted (multiomics). Initial bioinformatics analysis of multiomics data demonstrates differential gene expression in progenitor populations between Bap1 cKO and WT control. Ultimately, this model may provide better understanding the role and underlying mechanism of Bap1 in neurodevelopment.

**Disclosures:** C. Lim: None. S. Kim: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.26/B4

**Topic:** A.06. Developmental Disorders

**Support:** NIH/NIEHS R01ES029213

**Title:** Characterization of the role of the micropeptide NHIP in oxidative stress

**Authors:** \*J. L. HUANG<sup>1</sup>, H. YANG<sup>1</sup>, C. G. TORRES<sup>1</sup>, T. TRAN<sup>2</sup>, A. GOMEZ<sup>3</sup>, D. YASUI<sup>4</sup>, J. LASALLE<sup>5</sup>;

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**Abstract:** Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a complex etiology involving genetic, environment, and gene-environment interactions. The LaSalle lab recently discovered a novel gene, *NHIP* (neuronal hypoxia inducible, placenta), that has differential methylation in ASD placental samples. This is associated with decreased transcript levels in ASD brain samples. Assessing NHIP transcript levels in the human neuronal LUHMES cell line revealed increased expression following differentiation and exposure of differentiated neurons to hypoxia. The transcript encodes a micropeptide, as confirmed by immunofluorescent staining. Furthermore, the *NHIP* gene is conserved in primates, but not in other mammalian species. We hypothesize that *NHIP* plays a protective role during oxidative stress through its interaction with other proteins involved in gene regulation. To assess the role of NHIP in hypoxia-induced oxidative stress, we added exogenous NHIP peptide to LUHMES 24 hours prior to 1% hypoxia treatment and observed that ROS levels decreased with NHIP treatment. To determine the proteins that NHIP interacts with, we used affinity purification mass spectrometry and identified 121 putative NHIP-binding proteins from brain extracts. Many of these proteins are involved in transcription, translation, and neurodevelopmental disorders. Based on the predicted 3D structure of NHIP, it is possible that NHIP may be interacting with these proteins by mimicking a common transcriptional activation domain motif (9aaTAD). One of the potential NHIP-binding proteins is MeCP2, which is a protein whose dysfunction is responsible for the majority of Rett Syndrome cases. Rett Syndrome is a neurodevelopmental disorder that has

shared features with ASD. Many Rett Syndrome patients display breathing abnormalities that are associated with hypoxia. This presents the possibility that NHIP may interact with MeCP2 to promote proper hypoxia response and resolution. Characterization of NHIP and its binding partners will allow for evaluation of its potential use as a neuroprotective therapeutic in neurodevelopmental disorders such as ASD.

**Disclosures:** J.L. Huang: None. H. Yang: None. C.G. Torres: None. T. Tran: None. A. Gomez: None. D. Yasui: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 2C Biosciences. J. LaSalle: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 2C Biosciences.

## Poster

### PSTR201: Molecular Mechanisms Underlying Developmental Disorders II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.27/B5

**Topic:** A.06. Developmental Disorders

**Title:** Unraveling GNAI1-related epilepsies: variant analysis, cellular modeling, and targeted treatment

**Authors:** \*E. FATHI<sup>1</sup>, A. MIKOYAN<sup>2</sup>, K. NEMEC<sup>1</sup>, J. MANUEL<sup>1</sup>, S. SENGUPTA<sup>1</sup>, J. WANG<sup>1</sup>, E. ALMANZA FUERTE<sup>1</sup>, E. BONKOWSKI<sup>1</sup>, L. SADLEIR<sup>3</sup>, A. INNES<sup>4</sup>, M. BABU<sup>1</sup>, H. MEFFORD<sup>1</sup>;

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**Abstract:** Background: Pathogenic variants in *GNAI1* cause a developmental and epileptic encephalopathy (DEE) characterized by epilepsy, hypotonia, global developmental delay, severe speech impairment, and intellectual disability. *GNAI1* encodes  $G\alpha_{i1}$ , an inhibitory G protein  $\alpha$ -subunit that cycles between GDP-bound inactive and GTP-bound active states. Upon G-protein coupled receptor (GPCR) activation, GDP is exchanged for GTP, allowing  $G\alpha_{i1}$  to dissociate from the  $G\beta\gamma$  complex and regulate downstream signaling. To date, we have identified 27 unique, likely pathogenic variants in *GNAI1*, most of which are missense mutations affecting the GDP/GTP binding pocket. However, their functional impact remains unclear, limiting therapeutic development. **We hypothesize that pathogenic  $G\alpha_{i1}$  variants impair GTP binding, hydrolysis, and downstream signaling including cAMP levels.** Methods: Using purified proteins and fluorescent BODIPY-GTP analogue, we assessed the ability of mutant  $G\alpha_{i1}$  protein to bind and hydrolyze GTP. GPCR-mediated dissociation from  $G\beta\gamma$  was evaluated using TRUPATH BRET assay. Additionally, we employed FRET-based assay to measure inhibition of adenylyl cyclase and cAMP levels. To model  $G\alpha_{i1}$  dysfunction in a human neural context, we generated cortical brain organoids from patient-derived iPSCs carrying *GNAI1* mutations.

Results: Functional analysis of 25 variants via GTP analogue revealed three categories: (i) normal GTP hydrolysis (n=3), (ii) partial to complete loss of hydrolysis (n=14), and (iii) accelerated GTP hydrolysis (n=4). TRUPATH BRET identified three classes of variants with respect to GPCR activation: (i) increased G $\beta\gamma$  binding (n=14) that may result in sequestering of G $\beta\gamma$ ; (ii) complete unresponsiveness to GPCR activation (n=6); and (iii) partial dissociation defects (n=5). These disruptions are predicted to alter cAMP, mTOR, CREB, and MAPK/ERK pathways. FRET-based assays confirmed loss of G $\alpha_{i1}$ -mediated inhibition of adenylyl cyclase, leading to elevated cAMP. Early findings from patient-derived organoids demonstrate altered neuronal subtype composition. Conclusions: Our findings suggest that most G $\alpha_{i1}$  variants act via dominant-negative mechanisms, interfering with wild-type G $\alpha_{i1}$  function and normal signaling. As a potential therapeutic approach, we are testing allele-specific antisense oligonucleotides (ASOs) to selectively suppress the mutant *GNAI1* allele. Ongoing work using patient-derived organoids aims to validate functional consequences and therapeutic efficacy. Our findings highlight a critical role for G $\alpha_{i1}$  in neurodevelopment and support targeted therapies for *GNAI1*-related DEE.

**Disclosures:** E. Fathi: None. J. Manuel: None. S. Sengupta: None. J. Wang: None. E. Almanza Fuerte: None. E. Bonkowski: None. L. Sadleir: Other; LGS reports funding from Cure Kids New Zealand and the Health Research Council of New Zealand; and is a consultant for the Epilepsy Consortium.. M. Babu: None. H. Mefford: None.

## Poster

### PSTR201: Molecular Mechanisms Underlying Developmental Disorders II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.28/B6

**Topic:** A.06. Developmental Disorders

**Support:** NIH Grant R01 NS088479

**Title:** NMDA receptors in neurodevelopment and seizure pathogenesis

**Authors:** \*E. R. NEBET<sup>1,2,3</sup>, D. SAINI<sup>1,3</sup>, H. SIROTKIN<sup>1,2</sup>, L. P. WOLLMUTH<sup>1,2,3</sup>; <sup>2</sup>Neurobio. & Behavior, <sup>3</sup>Ctr. for Nervous Syst. Disorders, <sup>1</sup>Stony Brook Univ., Stony Brook, NY

**Abstract:** Seizures are the most frequently diagnosed neurological condition in pediatric patients with neurodevelopmental disorders (NDDs). Many of the genes implicated in seizure disorders both regulate neurodevelopment and play functional roles at synapses, though the contribution of these two processes to disease phenotypes is generally unknown. NMDA receptors (NMDARs) are glutamate-gated ion channels that regulate neurodevelopment and are central to excitatory neurotransmission in the brain. They are heterotetramers of two obligate GluN1 subunits, encoded by *GRIN1*, and typically two GluN2 subunits, GluN2A-D, encoded by *GRIN2A-D*. NDDs are prevalent in patients with disease-associated variants (DAVs) in the *GRIN* genes.

Notably, patients with DAVs in either *GRIN1* or *GRIN2A* often present with treatment-resistant seizures but the mechanistic basis for seizure propensity in these patients is unknown. To study NMDAR-associated seizure pathogenesis, we take advantage of zebrafish as a model organism because of their rapid development and high degree of NMDAR conservation relative to human NMDARs. To understand differing mechanisms that leads to seizures in patients with *GRIN1* versus *GRIN2A* variants, we are studying the complete loss-of-function of *grin1* (*grin1*<sup>-/-</sup>) or *grin2A* (*grin2A*<sup>-/-</sup>) in larval zebrafish. We measured seizure activity and susceptibility to chemoconvulsants, both in behavioral convulsive experiments and electrographically via local field potential recordings. We find that *grin1*<sup>-/-</sup> larval zebrafish exhibit increased activity in an acute seizure model. In contrast, *grin2A*<sup>-/-</sup> fish are more susceptible to the process of epileptogenesis. To explore the GluN2A-specificity of neurodevelopmental dysregulation in these animals, we measured expression of the potassium chloride cotransporter 2 (KCC2), which is a marker of neuronal maturation. Aligning with previous work from our group showing that KCC2 is downregulated in the absence of functional NMDARs, *grin2A*<sup>-/-</sup> larval fish likewise display decreased KCC2 expression in the forebrain, suggesting delayed neuronal maturation in these animals. As the upregulation of KCC2 during development is required for inhibitory GABAergic signaling in the mature brain, the loss-of-function of *grin1* or *grin2A* may cause putative GABA<sub>A</sub> receptor-mediated excitation, creating a pro-seizure state in the brain. Altogether, our data highlight the importance of NMDARs in regulating neurodevelopment and maintaining neurotypical activity balance in the brain.

**Disclosures:** E.R. Nebet: None. D. Saini: None. H. Sirotkin: None. L.P. Wollmuth: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.29/B7

**Topic:** A.06. Developmental Disorders

**Support:** GRF 115104620

**Title:** Maternal PM2.5 exposure induces behavioral deficits and hippocampal impairment in adult offspring independent to neuroinflammatory response

**Authors:** \*S. YAU;

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**Abstract:** merging evidence highlights air pollution as a significant environmental risk factor for autism spectrum disorders (ASD) in children, though the underlying mechanisms remain largely unclear. In this study, we investigated the effects of maternal exposure to the air pollutant PM2.5 on ASD-related behaviors, hippocampal plasticity, and neuroinflammatory responses in adult male and female offspring mice. Female C57BL/6J mice (6 weeks old) were exposed to PM2.5 via intratracheal instillation every three days for two weeks prior to mating, with exposure

continuing until birth. Both male and female offspring at 5 weeks of age exhibited reduced social novelty and increased repetitive behaviors; however, only male offspring showed significant impairment in working memory. PM2.5 exposure increased the number of proliferating progenitor cells and immature neurons in the hippocampus of male, but not female, offspring. Conversely, reduced dendritic length was observed only in female offspring. Both sexes displayed impaired long-term potentiation and decreased synaptic GluN2B protein expression following PM2.5 exposure. Notably, these alterations were not associated with neuroinflammatory responses in the hippocampus. Our findings suggest that maternal PM2.5 exposure impairs offspring behavior, potentially through hippocampal dysfunction, with sex-specific effects. Further research is warranted to elucidate the underlying mechanisms.

**Disclosures:** S. Yau: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.30/B8

**Topic:** A.06. Developmental Disorders

**Support:** JSPS KAKENHI Grant Number 25K11100

**Title:** Mitochondrial dysfunction in a patient with biallelic HPDL variants and the therapeutic potential of ketogenic diets

**Authors:** \*Y. NUMATA-UEMATSU<sup>1</sup>, M. UEMATSU<sup>2</sup>;

<sup>1</sup>Tohoku Univ. Hosp., Sendai, Japan; <sup>2</sup>Pediatrics, Tohoku Univ. Grad. Sch. of Med., Sendai / Miyagi, Japan

**Abstract:** Mitochondria play a critical role in maintaining white matter integrity, as evidenced by a group of disorders known as mitochondrial leukoencephalopathies. The advent of whole-exome sequencing has facilitated the discovery of numerous genes implicated in these conditions. Among them, biallelic variants in the HPDL gene, which encodes 4-hydroxyphenylpyruvate dioxygenase-like protein, have recently emerged as causative of a spectrum of neurodegenerative disorders. Clinical phenotypes range from neonatal-onset leukoencephalopathy with severe developmental impairment to juvenile-onset hereditary spastic paraplegia. Neuroimaging findings associated with HPDL mutations are highly variable, including white matter and striatal abnormalities, brainstem lesions, or even normal scans. We report a patient harboring novel compound heterozygous HPDL variants who presented with progressive leukoencephalopathy, bilateral putamen and brainstem lesions mimicking Leigh syndrome, and notable clinical improvement following a ketogenic diet. To elucidate the pathophysiology and therapeutic response, we performed cellular studies using patient-derived skin fibroblasts. First, we assessed mitochondrial function by measuring the oxygen consumption rate (OCR), a proxy for oxidative phosphorylation capacity. The OCR in the patient's fibroblasts

was significantly reduced compared to controls, indicating impaired mitochondrial respiration. To evaluate the effect of a ketogenic state, we supplemented the culture medium with  $\beta$ -hydroxybutyrate, a principal ketone body. However, this intervention did not improve OCR in vitro. HPDL catalyzes the conversion of 4-hydroxyphenylpyruvate to 4-hydroxymandelate, a precursor in the biosynthetic pathway of coenzyme Q10 (CoQ10), a key mitochondrial electron carrier. While CoQ10 supplementation is a conventional approach to mitochondrial dysfunction, its poor permeability across the blood-brain barrier limits its CNS efficacy. In contrast, ketone bodies readily cross into the brain, potentially supporting neuronal bioenergetics. Our findings suggest that although  $\beta$ -hydroxybutyrate failed to restore mitochondrial respiration in fibroblasts, the clinical improvement seen in vivo may reflect CNS-specific mechanisms not recapitulated in peripheral cell models. Further investigation using neuronal or brain organoid models derived from HPDL-mutant cells is needed to clarify the mechanistic benefits of ketogenic therapies and to develop more targeted interventions for mitochondrial leukoencephalopathies.

**Disclosures:** Y. Numata-Uematsu: None. M. Uematsu: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.31/B9

**Topic:** A.07. Development of Neural Systems

**Support:** NIH R01NS120832  
NIH U01NS099709  
NSF NeuroNex-1707352

**Title:** Hyperexcitation of locus coeruleus in early postnatal development results in distinct behavioral phenotypes

**Authors:** \*A. SILVAGNOLI<sup>1</sup>, M. TREE<sup>2</sup>, U. HOCHGESCHWENDER<sup>3</sup>;

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**Abstract:** The locus coeruleus (LC), the primary norepinephrine source in the central nervous system, undergoes critical postnatal refinement. Clinical associations link LC dysregulation to neurodevelopmental disorders including autism spectrum disorder and ADHD, though causal mechanisms remain unclear. We employed the ConVERGD dual-intersection genetic targeting strategy by transducing the LC in double-transgenic En1-Cre::Dbh-Flpo neonatal mice with AAV vectors to achieve LC-specific expression of luminopsin 11 (LMO11, GeNL\_SS-ChRmine), enabling bioluminescent optogenetic stimulation during early postnatal development by intraperitoneal injection of the luciferin cephalofurimazine (CFz) daily during P5-P15. Preliminary observations from adult LMO11-expressing luciferin-treated, i.e. LC hyperexcited subjects (n=3) reveal preferential occupancy of the open field periphery, suggesting increased

anxiety, and increased grooming and marble burying, indicators of stereotyped behavior, alongside reduced passive avoidance latency, suggesting impaired memory encoding. Motor function appears comparable between treated and non-treated groups based on rotarod performance. These early findings align with hypotheses implicating LC hyperactivity in neurodevelopmental pathogenesis. Data collection is ongoing for the full cohort (n=16 LMO11-expressing), with histological validation of LC activation patterns (c-Fos/adrenergic receptor co-labeling) and expanded behavioral analysis (social novelty). This study represents a novel approach for investigating developmental LC hyperactivity and its enduring consequences.

**Disclosures:** A. Silvagnoli: None. M. Tree: None. U. Hochgeschwender: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.32/B10

**Topic:** A.07. Development of Neural Systems

**Support:** NIH Grant R15ES036710

**Title:** The impact of sublethal maternal cyanotoxin ingestion on hypothalamic development in the mouse fetus

**Authors:** \*M. JANBAZI<sup>1</sup>, S. GHAJU<sup>2</sup>, S. M. MCANANY<sup>1</sup>, C. N. WOODY<sup>1</sup>, R. S. C. TAKESHITA<sup>3</sup>, W. C. J. CHUNG<sup>1</sup>;

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**Abstract:** Cyanobacterial harmful algal blooms are of major public health concern due to their release of cyanotoxins in freshwater lakes that are used for drinking water production. The most abundant type of cyanotoxins are microcystins (MC), which are well-established to cause liver toxicity. However, recent studies indicate that MCs may also be neurotoxic. The most toxic and abundant MC congener is MC leucine arginine (MC-LR). Recently, our laboratory determined that short-term ingestion of sublethal levels of MC-LR activated the hypothalamic paraventricular nucleus (PVN) neuroendocrine cells in young adult male mice in terms of  $\Delta$ FOSB immunoreactivity, corticotropin-releasing hormone, and vasopressin mRNA expression, and circulating levels of corticosterone. These neurons are part of the three-tiered hypothalamus-pituitary-adrenal (HPA) axis, which is known to activate and regulate the mammalian stress response. Most studies have investigated the toxic effects of MC-LR on adult animals. In contrast, little is known about the effects of maternal MC-LR ingestion on the embryonic development of the PVN. Here, we tested the hypothesis that fetal PVN development is disrupted following gestational maternal ingestion of sublethal MC-LR levels. For this purpose, female mice were timed-bred and gavaged daily with water (vehicle), 1  $\mu$ g/kg MC-LR, or 10  $\mu$ g/kg MC-LR for 12 or 18 gestational days. Our preliminary results showed that MC-LR ingestion for 12 or 18 days did not affect the dams' percent body weight change or mRNA expression of



inflammatory factors, such as tumor necrosis factor  $\alpha$ , interleukin-1 $\beta$ , and C-reactive proteins in the maternal liver. Similarly, no significant differences were detected in maternal plasma corticosterone levels between treatment groups. However, the crown-rump length (CRL) of the embryos, a parameter of fetal growth, showed that MC-LR significantly reduced CRL compared to vehicle-treated embryos. We will present data about the impact of maternal ingestion of sublethal MC-LR levels on fetal PVN cell proliferation and cell death. In addition, we will determine whether maternal MC-LR ingestion disrupts the development of corticotropin-releasing hormone PVN neurons, which are the most upstream activators of the HPA axis.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.33/B11

**Topic:** A.07. Development of Neural Systems

**Support:** NIH IRP HD008962  
NIH IRP HD008986  
NIH IRP HD001205  
NIH Scientific Director's Award  
NIH Intramural Research Fellowship

**Title:** Reducing methylation of histone 3.3 lysine 4 in the medial ganglionic eminence and hypothalamus recapitulates neurodevelopmental disorder phenotypes

**Authors:** J. LI<sup>1</sup>, A. TANZILLO<sup>2</sup>, G. PIZZIRUSSO<sup>3</sup>, A. CACCAVANO<sup>4</sup>, R. CHITTAJALLU<sup>5</sup>, Y. ZHANG<sup>6</sup>, K. A. PELKEY<sup>8</sup>, C. J. MCBAIN<sup>9</sup>, \***T. J. PETROS**<sup>7</sup>;

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**Abstract:** Methylation of lysine 4 on histone H3 (H3K4) is enriched on active promoters and enhancers and correlates with gene activation. Disruption of H3K4 methylation is associated with numerous neurodevelopmental diseases (NDDs) that display intellectual disability and abnormal body growth. Here, we perturb H3K4 methylation in the medial ganglionic eminence (MGE) and the hypothalamus, two brain regions associated with these disease phenotypes. These mutant mice have fewer forebrain interneurons, deficient network rhythmogenesis, and increased spontaneous seizures and seizure susceptibility. Mutant mice are significantly smaller than

control littermates, but they eventually became obese due to striking changes in the genetic and cellular hypothalamus environment in these mice. Perturbation of H3K4 methylation in these cells produces deficits in numerous NDD-associated behaviors, with a bias for more severe phenotypes in female mice. Single cell sequencing reveals transcriptional changes in the embryonic and adult brain that underlie many of these phenotypes. In sum, our findings highlight the critical role of H3K4 methylation in regulating survival and cell-specific gene regulatory mechanisms in forebrain GABAergic and hypothalamic cells during neurodevelopment to control network excitability and body size homeostasis.

**Disclosures:** J. Li: None. A. Tanzillo: None. G. Pizzirusso: None. A. Caccavano: None. R. Chittajallu: None. Y. Zhang: None. K.A. Pelkey: None. C.J. McBain: None. T.J. Petros: None.

## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.34/B12

**Topic:** A.06. Developmental Disorders

**Support:** 1RM1MH138313-01

**Title:** Single-cell and spatial transcriptomic phenotypes in a murine model of MYT1L-associated neurodevelopmental disorder

**Authors:** \*E. F. JONES<sup>1</sup>, S. CHATURVEDI<sup>1</sup>, T. LAW<sup>2</sup>, M. NEMERA<sup>2</sup>, R. D'SOUZA<sup>2</sup>, A. FENG<sup>2</sup>, J. JI<sup>2</sup>, R. CHASE<sup>1</sup>, H. GABEL<sup>2</sup>, J. D. DOUGHERTY<sup>1,3</sup>;  
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**Abstract:** Human genetics has revealed that pathogenic variants in transcription factors (TFs), crucial for gene regulation, can alter numerous neural gene programs, leading to neurodevelopmental disorders (NDDs) such as debilitating syndromic forms of autism spectrum disorder (ASD) and intellectual disability (ID). As part of the SSPsyGene consortium, which aims to characterize over 250 NDD-associated mutations, our data center (WU-SMAC) has generated our first matched single-cell (sc) and spatial RNA-seq data set for downstream analysis. The integration of these data types leverages spatial resolution for tissue organization and single-cell throughput, facilitating comprehensive gene expression profiling. Our model features a patient-variant-based mutation in the *Myt1l* gene, a TF with both activator and repressor roles essential for neuronal maturation. Pathogenic variants in *MYT1L* cause ASD and *MYT1L*-associated NDD, which is marked by behavioral disorders, language delay, ID, obesity, and epilepsy. Previous research on *Myt1l* function has focused on changes in the cortex, revealing that it acts early in development in a cell-specific manner, and *Myt1l* haploinsufficient mice exhibit impaired excitatory neuron differentiation. However, *Myt1l*'s cell-specific expression, TF cooperators, and activity have not yet been assessed in the entire adult mouse

brain across multiple regions. Here, we examine how *Myt1l*'s spatial expression and TF activity change across genotype and sex in both sc- and spatial RNA-seq data in *Myt1l* variant mice (n = 12), including the cortex, hippocampus, amygdala, thalamus, and hypothalamus, and explore how loss of *Myt1l* changes cell type migration and organization. We elaborate on how these pathways may contribute to NDD phenotypes in humans and identify putative targets for interventional strategies.

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## **Poster**

### **PSTR201: Molecular Mechanisms Underlying Developmental Disorders II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR201.35/B13

**Topic:** A.06. Developmental Disorders

**Support:** NIMH Grant 1RM1MH138313-01

**Title:** Systematic Analysis of Reinforcement Learning Across Genetic Models of Neurodevelopmental Disorders

**Authors:** \*S. E. MALONEY<sup>1</sup>, K. B. MCCULLOUGH<sup>3</sup>, M. GAIDICA<sup>4</sup>, R. CHASE<sup>5</sup>, H. OVIEDO<sup>2</sup>, H. GABEL<sup>6</sup>, A. V. KRAVITZ<sup>7</sup>, J. D. DOUGHERTY<sup>3</sup>;  
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**Abstract:** Neurodevelopmental and neuropsychiatric disorders, such as intellectual disability (ID), autism, and schizophrenia, are often characterized by learning challenges. Reinforcement learning tasks are particularly valuable in identifying deficits associated with these conditions. These tasks assess an animal's ability to utilize prior information to guide responses and adapt to changing rules, such as variable reinforcement schedules or reward probabilities. Consequently, these complex assessments hold promise for enhancing neuroscientists' ability to model ID in rodents, thereby enabling more robust mechanistic and interventional studies. In the past decade, significant progress has been made in identifying genetic variants linked to neurodevelopmental and psychiatric disorders. To elucidate the roles these genes play in reinforcement learning and decision-making, we are conducting behavioral phenotyping on over 100 mouse lines with prioritized mutations associated with these disorders, through the Washington University Scalable Mouse Assay Center, an Assay and Data Generation Center for the SSPsyGene consortium. Using scalable, home-cage based assays, we have assessed reinforcement learning and activity levels in several genetic risk models, including mutations in *Myt1l*, *Dnmt3a*, *Wac*,

*Nf1*, *Shank3b*, *Cdkl5*, *Cntnap2*, *Fmr1*, and *Znf292*. Wild type, heterozygous mutant, and homozygous mutant, when viable, littermates were assessed at 8-16 weeks of age. Samples sizes were 20 per genotype, split equally between males and females, and experimenters were blinded to genotypes during data collection. We evaluated performance with two-armed bandit-style learning tasks and a progressive ratio reinforcement learning task using the FED3 operant device in the home cage of single-housed mice. Additionally, we monitored 48-hour activity using a BEAM device in the home cage of single-housed mice to detect circadian rhythm alterations induced by these mutations. Our findings reveal similar and disparate effects of these mutations on decision making, flexibility, motivation, and activity levels. We found a reduction in accuracy in the bandit task and hyperactivity during the active phase in *Myt1l* mutants and a change in motivation levels in the *Dnmt3a* mutants. Overall, our standardized and scalable approach will enable the identification of convergent and distinct effects of these mutations. By further integrating our behavioral analysis with anatomical mapping and molecular assessments, we hope to uncover the relationship between behavioral changes and molecular brain changes induced by neurodevelopmental and neuropsychiatric genetic risk.

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## **Poster**

### **PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.01/B14

**Topic:** A.08. Adolescent Development

**Support:** R01DA057317

**Title:** Exploring behavioral and morphological of minor phytocannabinoids in zebrafish development

**Authors:** \*T. SHAMBLIN<sup>1,2</sup>, N. M. ASHPOLE<sup>2</sup>;

<sup>1</sup>Univ. of Mississippi, University, MS; <sup>2</sup>Envrn. Toxicology, Mississippi State Univ., Starkville, MS

**Abstract:** Studies have shown that human exposure to  $\Delta^9$ -tetrahydrocannabinidiol (THC), causes sex-dependent development deficits and persistent behavioral disorders, however, little is known on the developmental effects of cannabidiol (CBD) and other cannabis constituents - such as  $\Delta^8$ -THC and cannabigerol (CBG). We found similar developmental-behavioral endpoints in zebrafish exposed to THC. THC exposure resulted in dose-dependent hyperactivity and anxiety-like behavior (i.e., thigmotaxis) that persist well into adulthood. Therefore, we hypothesize that other minor cannabinoids will also impact behavioral and morphological development. Utilizing a zebrafish model for early development (6-96 hpf), photolocomotor and morphological responses were assessed following exposure to varying concentrations of minor

cannabinoids. Our results indicate  $\Delta 8$ -THC, CBD, CBG, hexahydrocannabinol (HHC), and tetrahydrocannabivarin (THCV) all significantly reduce photolocomotor response in a dose-dependent fashion. In comparison, cannabidiol (CBD), partial agonist of CB1 and CB2, elicited no behavioral changes even at the highest dose. Considering these effects, our lab is now exploring the mechanisms of action by which these minor phytocannabinoids alter behavior. We hypothesize that minor phytocannabinoids influence behavior primarily via activation of the CB2 receptor, considering its involvement in inflammatory pathways and skeletomuscular homeostasis. Prior studies have shown *Cnr2*, the zebrafish homolog of CB2, is expressed in zebrafish twenty-four hours post-fertilization (hpf) and has direct roles in zebrafish locomotor development and inflammatory cascades. To test this, we utilized an established transgenic *Cnr2* knockout (*Cnr2*<sup>-/-</sup>) line of zebrafish and exposed them to varying concentrations of minor phytocannabinoids of interest ( $\Delta 8$ -THC, THCV, CBD, CBG, CBN, HHC). Morphological defects and photolocomotor responses will be compared in larvae (120 hpf) that have been exposed during key stages of early development (6-96 hpf) - this analysis is, currently, ongoing. Finally, we'll continue exploring phytocannabinoids' mechanism of modulating behavior and morphology during development by observing the responses seen after knocking out *Cnr1* (the zebrafish homolog of CB1). Similar to *Cnr2*<sup>-/-</sup>, an established transgenic *Cnr1* knockout (*Cnr1*<sup>-/-</sup>) line of zebrafish will be utilized. The *Cnr1*<sup>-/-</sup> cohort will then be exposed using the same exposure paradigm used in the *Cnr2*<sup>-/-</sup> experiments. After which, morphology and photolocomotor responses will be compared to determine which receptor activation leads to observed toxicities seen in wild-type.

**Disclosures:** T. Shamblin: None. N.M. Ashpole: None.

## **Poster**

### **PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.02/B15

**Topic:** A.08. Adolescent Development

**Support:** CMCR Grant P64-07-001

**Title:** Effects of prenatal cannabidiol exposure on offspring behavior and development

**Authors:** \*I. F. FLEISCHER<sup>1</sup>, J. D. THOMAS<sup>2</sup>;  
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**Abstract:** In the U.S. and Canada, 20% of pregnant women report using cannabidiol (CBD), and pregnant women are two times more likely to receive a prescription for CBD than nonpregnant women. The high prevalence of CBD use among pregnant women is concerning, as little research has examined the effects of CBD on the developing fetus. The present study used an animal model of prenatal CBD exposure to explore effects in the exposed offspring. From gestational days 5-20, pregnant Sprague Dawley rats were exposed to 50 mg/kg/day CBD

dissolved in honey via an edible cookie dough ball. Offspring were tested in the open-field for 1 hr/day during the dark cycle, from postnatal days 30-33. Prenatal CBD exposure significantly reduced the number of pups born ( $p=.025$ ), and tended to increase the ratio of male-female pups ( $p=.069$ ). In the open field, subjects of both sexes exposed to prenatal CBD were hyperactive ( $p=.004$ ) at the beginning of the sessions. However, females exposed to prenatal CBD habituated slower to the open field than controls, remaining hyperactive throughout the first half of the session ( $p<.001$ ). Furthermore, prenatal CBD-exposed females were also more risk-taking, spending significantly more time in the center of the open field ( $p=.017$ ). These results highlight the risks of prenatal CBD exposure, particularly in female offspring. Given the high rates of CBD use among pregnant women, elucidation of the consequences of prenatal CBD on the fetus is necessary to inform public health initiatives that support safe and healthy pregnancies. Supported by CMCR P64-07-001.

**Disclosures:** I.F. Fleischer: None. J.D. Thomas: None.

## **Poster**

### **PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.03/B16

**Topic:** A.08. Adolescent Development

**Support:** Wisconsin Partnership Program at the University of Wisconsin School of Medicine and Public Health

**Title:** Early Adolescent Administration of a Gonadotropin-Releasing Hormone Agonist Alters Medial Amygdala Microglia in Female Rats

**Authors:** \*A. T. NGUYEN<sup>1</sup>, A. JOHNSON<sup>2</sup>, A. P. AUGER<sup>3</sup>;

<sup>1</sup>Univ. of Wisconsin-Madison, Madison, WI; <sup>2</sup>UW-Madison, Madison, WI; <sup>3</sup>Psychology, Univ. Wisconsin, Madison, Madison, WI

**Abstract:** Gonadotropin releasing hormone agonists (GnRHa), like leuprolide acetate (LA), are used to suppress puberty in individuals who may identify as transgender and non-binary (TNB). However, the implications of puberty blockers on adolescent brain development are less understood. Our previous findings indicated treatment with a GnRHa successfully delayed vaginal opening in females, decreased testosterone levels in males, and eliminated sex differences in rough-and-tumble (RTP) play behavior. LA is a GnRH analogue that acts as an agonist on GnRH receptors. While LA initially stimulates GnRH sensitive systems, sustained circulating levels result in desensitization via downregulation of GnRH receptors in the pituitary. Emerging literature suggests that during adolescent development, microglia play a critical role in regulation of sex specific development that may have lasting impacts of behavior. As microglia are known to modulate the development of sex differences in RTP, we hypothesized that treatment of LA would alter microglia quantity within the medial amygdala, a region involved in

RTP behavior. To test this, Sprague Dawley rats (20 male and 20 female) received either one injection of extended-release LA in depot suspension (12mg/kg) or vehicle on postnatal day (PND) 23 or PND 24. The day after LA treatment, RTP play behavior was assessed each day for ten days (PND 23-33). On PND 37 and 38, animals were perfused, and brains were processed for immunohistochemistry using an antibody targeting the microglia marker, Iba1. A two-way ANOVA indicated a main treatment effect ( $p = 0.036$ ), as well as an interaction effect of biological sex and treatment ( $p = 0.020$ ). Post-hoc tests indicated that females treated with LA had higher microglia cell counts than control females ( $p = 0.003$ ) within the amygdala. No difference in males were found, suggesting the effect of LA on microglia cell number is mainly occurring in females. Microglia cell counts in the medial amygdala did not correlate with duration or frequency of RTP behavior or non-RTP social behavior. These data suggest that microglia may serve as targets for understanding the role of hormonal blockade on sex differences in adolescent brain development and further investigation into cell morphology is required.

**Disclosures:** A.T. Nguyen: None. A. Johnson: None. A.P. Auger: None.

## **Poster**

### **PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.04/B17

**Topic:** A.08. Adolescent Development

**Support:** FAPERJ E-26/201.081/2022  
CNPq 408931/2024-8

**Title:** Varenicline reverses hippocampal neurotransmitter dysregulation induced by adolescent cigarette smoke in female mice: a metabolomic investigation

**Authors:** \*C. K. G. BRANDÃO, F. U. BRAGA, R. EFRAIM CORREA, A. L. N. FREITAS, Y. ABREU-VILLACA, A. C. MANHAES;  
Univ. do Estado do Rio de Janeiro, Rio de Janeiro, Brazil

**Abstract:** Adolescence is a sensitive period of neurobiological development marked by intense brain changes, including maturation of neurotransmitter systems. This heightened plasticity makes the adolescent brain particularly vulnerable to environmental influences, including exposure to psychoactive substances like nicotine, the primary addictive component of cigarettes. Early nicotine exposure has been linked to impairments in memory processes, emotional regulation, and behavioral control, with effects persisting into adulthood. Despite advances in tobacco control, adolescent smoking remains a significant public health concern, underscoring the need for effective therapeutic interventions. This study investigated the effects of adolescent cigarette smoke exposure on hippocampal neurochemistry in Swiss mice and the modulatory role of varenicline, a partial agonist of  $\alpha 4\beta 2$  nicotinic receptors used in adult tobacco

dependence treatment. Ninety-six mice (both sexes) were exposed daily to cigarette smoke (0.73 mg nicotine; SMK) or air (CNT) from postnatal day (PN) 30 to PN45 for 8h/day, followed by varenicline (VAR) or vehicle (VEH) treatment. At PN41, treatment with VAR (0.5 mg/kg/bid v.o.) or VEH was initiated, and from PN46 to PN56, the dose was doubled. Half of the animals were analyzed during treatment (PN56) and half 30 days later. Neurochemical analyses via LC-MS/MS assessed levels of neurotransmitters and precursors related to cholinergic, catecholaminergic, serotonergic, and glutamatergic systems. Results showed significant neurochemical alterations in SMK female mice. These included reductions in phenylalanine, tyrosine, noradrenaline, glutamate, glutamine, GABA and tryptophan levels. The study indicates widespread disruption across excitatory and inhibitory pathways, as well as neurotransmitter systems involved in mood and stress regulation. Importantly, varenicline treatment restored these neurochemical levels to near-control values, implying a neuroprotective effect. These findings suggest that adolescent cigarette smoke exposure induces broad, sex-specific hippocampal neurochemical changes affecting synaptic plasticity, cognition, and emotional regulation pathways in females. The reversal of these effects by varenicline highlights its potential therapeutic value beyond smoking cessation, particularly for the developing brain and considering sex-specific vulnerabilities. Overall, this work advances understanding of the neurochemical impact of early nicotine exposure and supports pharmacological strategies adjusted to adolescents and sex-specific neurobiological contexts.

**Disclosures:** C.K.G. Brandão: None. F.U. Braga: None. R. Efraim Correa: None. A.L.N. Freitas: None. Y. Abreu-Villaca: None. A.C. Manhaes: None.

## **Poster**

### **PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.05/B18

**Topic:** A.08. Adolescent Development

**Support:** FAPERJ E26/210.246/2022  
CNPq 433018/2016-0

**Title:** Behavioral effects of varenicline treatment in animal model of e-cigarrete exposure in adolescent Swiss mice

**Authors:** \*F. U. BRAGA<sup>1</sup>, V. DUARTE<sup>2</sup>, C. BRANDÃO<sup>4</sup>, G. SOUZA<sup>3</sup>, Y. ABREU-VILLACA<sup>5</sup>, A. C. MANHAES<sup>6</sup>;

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**Abstract:** The prevalence of electronic cigarette (EC) use has been increasing significantly worldwide, particularly among adolescents. Despite the alarming rise in adolescent EC use, there is a notable paucity of studies investigating the neurobehavioral consequences of EC vapor exposure in this age group, as well as limited research on pharmacological interventions for cessation. Here we tested the effects of varenicline—a partial agonist at  $\alpha 4\beta 2$  nicotinic acetylcholine receptors and a full agonist at  $\alpha 7$  receptors—on behavior expressed in the elevated plus maze (EPM) and novel object recognition (NOR) tests by adolescent mice previously exposed to electronic cigarette vapor (VAPE). To simulate VAPE exposure, animals were transported daily to a custom-built equipment (La Jolla Alcohol Research, Inc., CA, USA) or to a filtered air exposure chamber (CONTROL). VAPE containing nicotine (24 mg/mL) dissolved in a vehicle composed of propylene glycol and vegetable glycerin at a 60:40 ratio was produced using a 1.8  $\Omega$  single coil EC (VandyVape BSKR B3 MTL RTA). From postnatal day 30 (PN30) to PN45, VAPE animals were subjected to two daily exposure cycles of 2h each, with a 2-h interval between cycles, totaling 4h of daily exposure. Half of the VAPE animals were administered varenicline (Sigma-Aldrich) diluted in Milli-Q water via gavage twice daily (12-h interval; VAPEVAR animals). A total daily dose of 1 mg/mL was administered from PN40 to PN45 (during the exposure period), followed by 2 mg/mL from PN46 to PN56 (after the exposure period). The other half of the VAPE and all CONTROL animals received only filtered water. Behavioral assessments were conducted at one of two ages: at the conclusion of treatment (EPM: PN53; NOR: PN55) or at ten days post-treatment (EPM: PN63; NOR: PN65). In the EPM, at PN53, anxiety-like behavior increased in VAPEVAR females when compared to the respective CONTROL group (+11%,  $p=0.018$ ). Regarding decision-making, VAPE males showed a reduction in this behavior when compared to CONTROL (-20%,  $p=0.026$ ) and VAPEVAR (-20%,  $p=0.027$ ) animals. In the NOR, at PN65, VAPEVAR animals showed a reduction in the preference for the new object when compared to CONTROL (interaction time: -14%,  $p=0.025$ ; number of interactions: -13%,  $p=0.023$ ) and VAPE animals (interaction time: -13%,  $p=0.054$ ; number of interactions: -13%,  $p=0.022$ ). Results show that VAR corrected the effects on decision making of VAPE exposure in PN53 males tested in the EPM. However, VAR also showed age- or sex-dependent behavioral alterations, depending on the test that was used. A neurochemical study is warranted to better understand the mechanisms associated with the observed behavioral alterations.

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## **Poster**

### **PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.06/B19

**Topic:** A.08. Adolescent Development

**Support:** FAPERJ E-26/201.081/2022  
CNPq 433018/2016-0

**Title:** Effects of perinatal E-cigarette exposure in Swiss mice: a behavioral approach

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**Abstract:** Tobacco consumption is one of the main causes of preventable death in the world. While overall combustible cigarette smoking rates have declined over the last decade, the rising popularity of E-cigarettes has led to concerns regarding the perpetuation of nicotine use. E-cigarette is often marketed as a smoking cessation tool or harm reduction product, yet young adults rarely use E-cigarettes for these purposes. Use of noncombustible nicotine products by pregnant mothers, which exposes the developing fetus to nicotine, a known teratogen, is increasing. In addition, young children are frequently exposed to secondhand nicotine aerosols generated by E-cigarettes, with little understanding of the effects these exposures can have on health. The aim of this work was to investigate the behavioral effects of perinatal exposure to E-cigarettes on Swiss mice dams and their litters. These effects were observed through: 1) assessment of maternal care using the pup retrieval test (PRT); 2) assessment of anxiety-like behaviors in the elevated plus maze (EPM); 3) assessment of novelty-seeking behavior in the hole board (HB) test. This study used 20 three-month old, virgin female Swiss mice. These females were caged with male mice at the ratio of 2:1. After mating, each female was placed in an individual cage until delivery. Two days after birth (PN2), litters were culled to 6 pups (3 male and 3 female). The dams and their litters were randomly assigned to nicotine or control groups. Nicotine group animals were exposed to E-cigarette aerosol (equipment from La Jolla Alcohol Research Inc, CA, USA) from postnatal day 3 to 21. Animals were placed in the machine daily for a total of 4 h (two-hour sessions with 2 h intersession interval). The nicotine exposure was made with a nicotine solution (48 mg/ml) diluted in vehicle (isopolypropylene glycol and vegetable glycerin 4:6). A 1.8  $\Omega$  single coil E-cigarette (VandyVape BSKR B3 MTL RTA) was used to produce the aerosol. Control group animals were exposed to the same environment, but without the nicotine vapor. At PN4 dams were tested using the pup retrieval test (PRT). From PN22 to PN26 animals were tested respectively on the EPM and HB hole board tests. Results: In the PRT, E-vape dams showed reduced the retrieval time (-49%,  $p = 0.004$ ) in comparison to controls. In the EPM, E-vape pups (PN22) showed a decrease (-20%,  $p = 0.034$ ) in closed arm entries. In the HB, male E-vape pups (PN26) showed a reduced (-24%,  $p < 0.006$ ) number of nose-pokes. Our data indicate that the exposure to vapor generated from E-cigarettes increased maternal behavior, as measured by PRT, and, in the pups, reduced total locomotor activity in the EPM and novelty-seeking behavior in the HB.

**Disclosures:** V.H.S. Duarte: None. C. Brandão: None. R. Simeão Correia Douets: None. I. Bertasso: None. N. Serpa: None. Y. Abreu-Villaca: None. Y. Tizabi: None. P. Lisboa: None. A.C. Manhaes: None.

**Poster**

**PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.07/B20

**Topic:** A.08. Adolescent Development

**Support:** TRDRP Grant T34IP8023

**Title:** Impact of Prenatal E-Cigarette Exposure on Neurodevelopment and Long-Term Behavioral Patterns

**Authors:** \*K. WANG, M. PALANIAPPAN, C. D. FOWLER, V. LALLAI;  
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**Abstract:** E-cigarette usage has increased significantly within recent years, due to the assumption that it is a safer alternative to traditional cigarettes. With the increase in accessibility to new aerosolized substances such as nicotine and THC, e-cigarettes have introduced new concerns and has gained popularity among individuals in reproductive ages, including pregnant women. With e-cigarette use rising among pregnant individuals, concerns have grown regarding its potential consequences on offspring behavior, yet findings have been inconsistent, particularly regarding sex differences. Previous studies suggest how prenatal e-cigarette exposure, specifically to nicotine and THC, can disrupt dopamine signaling, alter synaptic plasticity, and increase susceptibility to substance use disorders later in life. Using a prenatal vape exposure model, this study systematically examines the effects of prenatal nicotine and/or THC exposure on offspring social behavioral responses analyzing potential sex-specific as well as long term effects using ultrasonic vocalization, social interaction tests. Changes in social exploratory and distress-like behaviors were observed between sexes and treatments. These findings emphasize the complex and sex-specific nature of prenatal e-cigarette effects, suggesting that biological and environmental factors interact to shape long-term behavioral outcomes.

**Disclosures:** K. Wang: None. M. Palaniappan: None. C.D. Fowler: None. V. Lallai: None.

## **Poster**

### **PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.08/B21

**Topic:** A.08. Adolescent Development

**Support:** TRDRP T31IP1427C  
TRDRP T33IP617  
TRDRP T34IR8049

NIH R01 DA048899  
NIH T32 DA050558

**Title:** Developmental and sex-dependent effects of a human *CHRNA6* 3'-UTR SNP on nicotine-induced behaviors and tyrosine hydroxylase expression in rats

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**Abstract:** Adolescence is a critical period for brain development and often coincides with initiation of substance use, highlighting the importance of identifying neurobiological and genetic factors that contribute to drug vulnerability. Although genome-wide studies have revealed genetic variants linked to various diseases, the role of genetic predisposition in adolescent substance use remains underexplored. A single nucleotide polymorphism (SNP) in the 3'-untranslated region (3'-UTR) of the *CHRNA6* gene, which encodes the  $\alpha 6$  nicotinic receptor subunit, has been associated increased nicotine use. To investigate the functional significance of this variant (rs2304297), we engineered humanized rat models carrying the human *CHRNA6* 3'-UTR SNP ( $\alpha 6^{CC}$  and  $\alpha 6^{GG}$ ). Prior work revealed sex and genotype dependent effects of nicotine on behavior and neurochemistry in adolescent rats. In the present study, we examined how four days of nicotine pretreatment (2 x 30  $\mu$ g/kg nicotine, i.v.) impacts behavior and dopamine-related protein expression in the critical ventral tegmental area (VTA) and nucleus accumbens (NAc) in both adolescent and adult human *CHRNA6* 3'-UTR SNP rats. Nicotine enhanced locomotor activity in adolescent female  $\alpha 6^{CC}$  rats and male  $\alpha 6^{GG}$  rats, while only adult female  $\alpha 6^{CC}$  rats showed this effect. Western blot analysis revealed higher tyrosine hydroxylase (TH)-a marker of dopamine synthesis- in the VTA of adolescent male  $\alpha 6^{GG}$  rats compared to  $\alpha 6^{CC}$  counterparts, independent of drug exposure. Further characterization in drug-naïve adolescent rats showed increased TH protein expression via western blot and a greater number of dopaminergic neurons via immunohistochemistry in the VTA of female  $\alpha 6^{CC}$  and male  $\alpha 6^{GG}$  rats compared to their respective counterparts. These findings reveal age-, sex-, and genotype-dependent effects of the human *CHRNA6* 3'-UTR SNP on nicotine-induced behavior and TH protein expression. Since TH regulates dopamine biosynthesis, its upregulation during adolescence may contribute to enhanced reward sensitivity and reinforcement. Taken together, our data suggests that this SNP modulates dopamine-related pathways in a manner that may influence susceptibility to substance use.

**Disclosures:** E.M. Castro: None. F.M. Leslie: None. S. Lotfipour: None.

**Poster**

**PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.09/B22

**Topic:** A.08. Adolescent Development

**Support:**

NIH Grant 5R03AA031378

**Title:** The impact of cumulative prenatal and adolescent alcohol exposure on domains of executive function

**Authors:** \*C. M. SIDE<sup>1</sup>, G. E. KIRKPATRICK<sup>2</sup>, Z. JOSHLYN<sup>3</sup>, H. TREVATHAN<sup>3</sup>, S. GIANG<sup>3</sup>, S. M. MOONEY<sup>4</sup>, D. L. ROBINSON<sup>5</sup>;

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**Abstract:** According to the CDC, 40% of pregnant women who reported drinking within the past 30 days did so at binge levels. Additionally, alcohol is one of the most widely used substances during adolescence, with 8.6% of 12- to 20-year-olds reporting binge drinking within the past month. Recently, researchers proposed three latent variables of executive function impacted by developmental binge drinking: behavioral flexibility, working memory, and inhibition. Our groups have published data showing that, independently, prenatal alcohol exposure (PAE) and adolescent alcohol exposure (AAE) reduced behavioral flexibility on the attentional set shift task (ASST), where PAE rats took more trials to reach criterion in all phases of the ASST and AAE rats showed impaired reversal learning. Currently, it is unknown how the cumulative effects of PAE and AAE impact executive function. Thus, we sought to characterize the impact of a “double-hit” of PAE + AAE on different domains of executive function. To do this, Sprague Dawley dams (n=4; 50% ethanol) were given either 2.25 g/kg of ethanol (25% w/v, I.G.) or water twice a day between gestation days 13.5 and 20.5. Offspring were given either 5.0 g/kg ethanol (25% w/v, I.G.) or water on a 2-days-on, 2-days off schedule between postnatal days (P) 25 and 54. On P70, male and female offspring were lightly food restricted and continued throughout the duration of the experiment. On P84-104, rats underwent a behavioral battery, including low-light elevated plus maze (LL-EPM), ASST, spontaneous alternations, and novel object recognition. Data from LL-EPM showed that of the time spent in the arms, PAE animals with or without AAE spent significantly more time in the open arms and made more entries, suggesting increased disinhibition facilitated by low-light conditions. Additionally, data from ASST showed that PAE animals performed significantly worse during reversal 1, suggesting potential deficits in behavioral flexibility. There were no significant differences in novel object recognition or spontaneous alternations. Preliminary neurochemical data shows a significant reduction in choline acetyltransferase (ChAT) reactivity in the medial septal nuclei for both PAE and AAE. Future research will focus on potential neurochemical markers in regions associated with the domains of executive function, such as the prelimbic and infralimbic cortices, using IHC. Together, these results help us to understand the unique ways in which cumulative developmental alcohol exposure impacts adult behavioral flexibility and impulsivity.

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**Poster****PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.10/B23

**Topic:** A.08. Adolescent Development

**Title:** Does early-life steroid exposure alter the hpg axis: a focus on kisspeptin neurons

**Authors:** \*C. K. SOLOMON<sup>1</sup>, C. KOJIMA<sup>2</sup>, B. WHITLOCK<sup>3</sup>;

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**Abstract:** Reproductive control using exogenous hormones is common in humans, but surgical gonadectomy remains the standard in animals. Ovariectomy in females is invasive and painful, requiring anesthesia, surgical tools, a sterile environment, and trained personnel. Non-surgical alternatives could reduce animal discomfort, and the resources needed for sterilization. Previous studies in rodents and, more recently, male pigs have shown that administering exogenous sex steroids during the neonatal period can induce long-term or permanent infertility. These findings have prompted efforts to understand how early steroid exposure disrupts reproductive function. One likely mechanism involves the kisspeptin (KP) system, a critical regulator of the hypothalamic-pituitary-gonadal (HPG) axis. KP, encoded by KISS1, is produced by KNDy neurons in the arcuate nucleus (ARC) and KP neurons in the preoptic area or anteroventral periventricular nucleus, and it drives gonadotropin-releasing hormone (GnRH) secretion. Disruption of KP signaling impairs GnRH release, reducing downstream luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Given the steroid sensitivity of KP neurons and their central role in reproduction, it is logical to hypothesize that this system mediates the long-term effects of neonatal steroid exposure on fertility. This study examines the impact of exogenous sex steroids administered during the 3-week “mini puberty” neonatal period on KP neurons in female pigs. We hypothesize that steroid exposure will reduce ARC KP neurons, disrupt the HPG axis, and impair fertility. Six neonatal pigs (PND 3) were treated subcutaneously with either a sham implant (CTRL, n = 3) or estradiol (16 mg) + trenbolone acetate (80 mg) (E/TBA, n = 3; Relavor®-S, Merck). Weekly blood samples were collected for hormone analysis [LH, FSH, anti-Müllerian hormone (AMH), and sex steroids], and brains were collected at ~PND24 for KP immunohistochemistry. We expect fewer ARC KP neurons in the E/TBA group. We also anticipate reduced LH and FSH due to KP suppression, and lower AMH due to direct or indirect effects on the ovaries. Circulating sex steroid levels may differ in the treated group, though some effects may not emerge within the study’s timeframe. This work supports the development of humane, hormone-based alternatives to surgical sterilization by targeting key neuroendocrine pathways.

**Disclosures:** C.K. Solomon: None. C. Kojima: None. B. Whitlock: None.

**Poster**

**PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.11/B24

**Topic:** A.08. Adolescent Development

**Support:** Building Strength Grant, BGSU

**Title:** Perinatal Exposure to Brain Health Supplements Affects Brain Development and Behavior

**Authors:** \*H. RUBY<sup>1</sup>, J. WILLING<sup>2</sup>;

<sup>2</sup>Psychology, <sup>1</sup>Bowling Green State Univ., Bowling Green, OH

**Abstract:** There is a tremendous amount of research investigating supplements that slow cognitive decline in aged populations. Two supplements popular within this field—nicotinamide mononucleotide (NMN) and resveratrol—are particularly notable due to their ability to reduce neural apoptosis in rodent models of aging. These supplements are also recognized and marketed for being beneficial to overall brain health and may benefit pregnant mothers due to their anti-inflammatory properties. However, the consumption of these nutraceuticals raises concerns, as they can cross the placenta and affect with the developing fetus. Thus, perinatal exposure to these supplements may alter fundamental developmental processes, including apoptosis, which is essential for the organization of neural circuits. In the present study, we divided Long Evans dams into four exposure groups: NMN-exposed animals, resveratrol-exposed animals, animals exposed to both supplements, and control animals. Dosing began on embryonic day 0 (E0) and continued until postnatal day 10 (P10). Neonatal behavioral tests were conducted on P5, P7, and P10 to assess the sensorimotor capabilities of the exposed offspring. In littermates, adult behavioral testing occurred on P80 to observe possible long-lasting effects on hippocampal and PFC-regulated behaviors. Total brain and body weights were collected during the neonatal period and in middle adulthood (P110). Results suggest that perinatal exposure to these supplements affects not only early locomotor behaviors and body weights, but also continues to influence body weights into middle adulthood (P110). Interestingly, perinatal exposure to resveratrol, alone or in combination with NMN, increases adult brain weights even after accounting for differences in body weights. Additional data on fecundity, litter size, and sex ratios were also collected. Histological investigations into the exact mechanisms responsible for differing brain weights include cell counts and cortical volumes. The findings from this study have implications for the recommendation of supplements during pregnancy and enhance our understanding of how perinatal exposures affect brain functioning throughout the lifespan.

**Disclosures:** H. Ruby: None. J. Willing: None.

**Poster**

**PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.12/B25

**Topic:** A.08. Adolescent Development

**Support:** This project was supported by a sponsored research project from GATC Health.

**Title:** Targeting Opioid Use Disorder through AI-Designed Serotonergic Modulators

**Authors:** \*V. LALLAI<sup>1</sup>, S. KHO<sup>2,6</sup>, A. MARTIN<sup>3</sup>, J. FOWLER<sup>1</sup>, M. ROACH<sup>7</sup>, K. WANG<sup>1</sup>, M. R. BAUTISTA<sup>1</sup>, M. PALANIAPPAN<sup>9</sup>, A. MOGUL<sup>1</sup>, T. G. MORRIS<sup>8</sup>, V. NARAYAN<sup>4</sup>, W. LERNHARDT, PHD<sup>5</sup>, J. LAKEY<sup>5</sup>, A. R. ZAVALA<sup>8</sup>, C. D. FOWLER<sup>1</sup>;  
<sup>1</sup>Univ. of California, Irvine, Irvine, CA; <sup>2</sup>GATC, Fullerton, CA; <sup>3</sup>GATC, Morgantown, WV;  
<sup>4</sup>GATC, SOUTH JORDAN, UT; <sup>5</sup>GATC, Irvine, CA; <sup>6</sup>GATC Hlth., Irvine, CA; <sup>8</sup>Psychology,  
<sup>7</sup>California State Univ., Long Beach, CA; <sup>9</sup>Univ. of California, Irvine, Irvine, CA

**Abstract:** AbstractThe opioid epidemic continues to demand innovative treatment strategies. Many individuals with opioid use disorder (OUD) struggle to maintain abstinence due to the reinforcing effects of powerful opioids like fentanyl. In this study, we utilized an artificial intelligence (AI)-driven drug discovery platform to develop novel therapeutic candidates targeting serotonergic signaling. Based on predicted receptor profiles and human postmortem brain data, two compounds, compound-021 and compound-1021, were synthesized and validated *in vitro*. Compound-1021 showed high target specificity and favorable blood-brain barrier permeability. Using a fentanyl intravenous self-administration (IVSA) model in male and female rats, we found that compound-1021 significantly reduced drug intake without affecting locomotion or producing adverse behavioral effects. Unlike classical psychedelics, compound-1021 targets serotonin receptors without triggering hallucinogenic or disruptive behavioral responses. Additionally, it enhanced dendritic spine plasticity in brain regions involved in reward processing. These results validate the AI-guided, polypharmacy-focused discovery strategy and identify compound-1021 as a promising, non-opioid therapeutic candidate for reducing fentanyl use. Further investigation will explore its long-term efficacy and safety.

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**Poster**

**PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.13/B26

**Topic:** A.08. Adolescent Development

**Support:** Funding from Department of Biology & Chemistry, Liberty University

**Title:** Offspring affective behavioral and neurobiological outcomes influenced by maternal dietary patterns



**Authors:** \*A. FROMMACK, C. YEAGER, S. NELSON, M. PINO, IV, R. OOI, K. LONG, K. GILLEY;  
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**Abstract:** Maternal diet has shown to have a profound impact on offspring. Reports underscore the detrimental influence of a prenatal Western Diet (WD) on offspring development, indicating increased reports of anxiety and depression. However, few studies have examined the potential neurodevelopmental benefits of health-promoting diets such as the Mediterranean Diet (MD). The present study aims to elucidate the influence of prenatal dietary composition on offspring affective behavioral and neurobiological outcomes. We hypothesized that prenatal MD exposure will be protective against the onset of offspring anxiety- and depressive-like behaviors and will enhance dendritic arborization. Conversely, we expected that maternal WD consumption would predispose offspring to increased affective disturbances and reduced dendritic arborization. The study implemented a 2 (sex) x 4 (diet) factorial design. The 4 dietary groups consist of WD, MD, and two control diets, including a purified diet control (PC) to match the macro-nutrient composition of the WD and a chow control (CC) that matches the MD composition. Behavioral assessments for affective dysregulation included Marble Burying (MB) to assess anxiety-like behavior through excessive burying and the Forced Swim Test (FST), evaluating behavioral despair in reduced active swimming. 2-way ANOVAs were used to assess significance. MB results show a significant reduction in burying for WD males compared to WD females ( $p = .012$ ) and CC females ( $p = .048$ ) in MB. While hypo burying is not presently well characterized, this may indicate reduced motivation associated with a depressive-like phenotype as depression is dynamic. In the FST, heightened immobility was observed in PC males ( $p = .032$ ), PC females ( $p = .017$ ), and WD females ( $p = .004$ ) when compared with CC females. Interestingly, FST results indicate a potential depressive-like phenotype for the WD and PC groups, not contingent on sex. Brain data are inconclusive until further analyses are performed. Contrary to expectations, present data does not suggest a benefit for prenatal MD exposure; however, underlying benefits may be yet revealed in the presence of a “second hit” model that introduces a stressor to evaluate resilience. This data could serve as a launching point for further mechanistic studies. Previous reports have indicated that affective changes may be associated with reduced dendritic arborization in the hippocampus and amygdala, which should be considered moving forward. This research hopes to aid the clinical and public health fields by providing relevant lifestyle-based evidence to support their counsel and clinical practice.

**Disclosures:** A. Frommack: None. C. Yeager: None. S. Nelson: None. M. Pino: None. R. Ooi: None. K. long: None. K. Gilley: None.

## **Poster**

### **PSTR202: Early Life Vulnerability**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR202.14/B27

**Topic:** A.08. Adolescent Development

**Support:** Funding from Department of Biology & Chemistry, Liberty University

**Title:** Offspring cognitive and neurobiological outcomes influenced by maternal dietary patterns

**Authors:** \*S. NELSON, A. FROMMACK, C. YEAGER, M. PINO, IV, R. OOI, K. LONG, K. GILLEY;  
Liberty Univ., Lynchburg, VA

**Abstract:** Maternal nutrition plays a critical role in shaping offspring neurodevelopment. Current research heavily highlights the detrimental effects of a prenatal Western Diet (WD) on offspring development, highlighted in areas of metabolism, mood disorders, and cognition, but little research has focused on health-promoting diets, such as the Mediterranean Diet (MD), particularly within a preclinical model. The present study investigates how prenatal diet influences offspring behavior and brain outcomes, post-mortem analyses focusing on hippocampal volume and arborization. We hypothesized that prenatal MD exposure would enhance cognitive performance and hippocampal morphology relative to controls, while prenatal WD exposure would be associated with impairments in those same areas. Given that clinical studies frequently report differences in severity of mood and cognitive outcomes as dependent on sex, both male and female offspring were evaluated in our study. Using a C57BL/6J mouse model, we employed a 2 (sex)  $\times$  4 (diet) factorial design, with dietary groups including WD, MD, a purified control (PC) matched to the WD's macronutrient profile, and a chow control (CC) aligned with the MD. Behavioral testing began at 7 weeks of age and included Conditional Associative Learning (CAL) to assess executive function and decision-making, as well as the Water Maze (WM) to evaluate spatial learning and long-term memory. Following behavioral assessments, hippocampal tissue was processed using Golgi-Cox staining to analyze hippocampal volume, dendritic morphology. Although data collection is ongoing to ensure adequate statistical power, while preliminary data is inconclusive ( $ps > .05$ ), as more mice are included to reach an n of 10mice/group for sufficient power we expect preliminary trends suggesting that prenatal MD may confer cognitive and structural benefits to reach significance. Findings may provide potential translational relevance for dietary recommendations during pregnancy. While we recognize that maternal nutrition is discussed with patients, often this revolves around food-avoidance with little to no support for promoting healthy habits. Our results may then support the development of evidence-based guidelines advocating for positive maternal nutritional changes to promote beneficial neurodevelopmental and mental health outcomes in children.

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**Poster**

**PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.01/B28

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

**Support:** CIHR Foundational Grant to BAO

**Title:** Surgery under inhaled anesthesia upregulates  $\alpha 5\text{GABA}_A$  receptor expression and dysregulates inhibitory synaptic signalling in CA1 pyramidal neurons

**Authors:** \*H. FANG<sup>1</sup>, D.-S. WANG<sup>2</sup>, C. BRENNAN<sup>1</sup>, B. A. ORSER<sup>3</sup>;  
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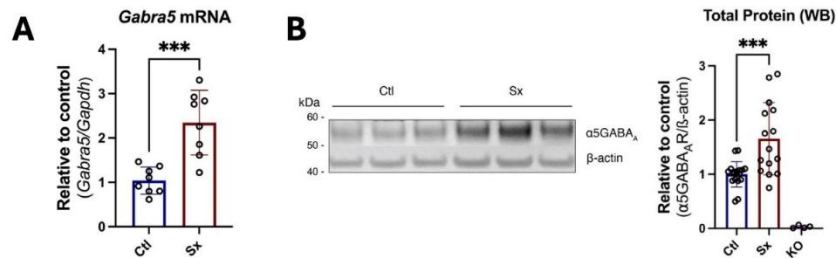


**Fig.** Surgery increases the expression of  $\alpha 5\text{GABA}_A$  and dysregulates hippocampal inhibitory synaptic neurotransmission. (A) Surgery increases the expression of *Gabra5* transcripts in murine hippocampal neurons (n = 16 mice, 8 Sx, 8 Ctl; p = 0.0004). (B) Representative Western blot and summarised data of total  $\alpha 5\text{GABA}_A$  protein (n = 18 mice, 6 Ctl, 10 Sx, 2 *Gabra5*<sup>-/-</sup> p < 0.0001). \*P < 0.05, \*\*P < 0.01, \*\*\*p < 0.001. Data are mean  $\pm$  SD and analysed using an unpaired t-test for (A) and ordinary one-way ANOVA for (B).

**Abstract:**

Perioperative neurocognitive disorders (PNDs) are among the most common adverse outcomes of surgery.  $\alpha 5$  subunit-containing  $\gamma$ -aminobutyric acid type A receptors ( $\alpha 5$ GABA<sub>A</sub>Rs) are predominately localized extrasynaptically in hippocampal neurons and play a key role in cognition. We previously showed that general anesthesia alone increases  $\alpha 5$ GABA<sub>A</sub>R surface expression and function without altering total protein or mRNA levels. These changes were associated with persistent cognitive deficits, which were absent in *Gabra5*<sup>-/-</sup> mice and were prevented by pharmacological inhibition of  $\alpha 5$ GABA<sub>A</sub>Rs. However, the combined effects of surgery and anesthesia on  $\alpha 5$ GABA<sub>A</sub>Rs remain unclear. Here, we investigated the effects of surgery and anesthesia on the expression and function of  $\alpha 5$ GABA<sub>A</sub>Rs. Adult male (9-12 weeks) C57BL/6 mice underwent laparotomy under sevoflurane anesthesia (2.5-4%). Hippocampi were extracted 24 and 72 h after surgery for mRNA and protein quantification, respectively. Further, coronal hippocampal slices were prepared 72 h after surgery and miniature inhibitory post-synaptic currents (mIPSCs) were recorded from CA1 pyramidal neurons using whole-cell patch-clamp technique. Surgery significantly increased the mRNA (Fig. A) and total protein (Fig. B) expression of  $\alpha 5$ GABA<sub>A</sub>Rs. Furthermore, preliminary electrophysiological data show reduced mIPSC frequency, decreased amplitude, and no change in area or kinetics. These findings indicate that surgery upregulates  $\alpha 5$ GABA<sub>A</sub>Rs in hippocampal neurons and disrupts synaptic inhibition. Ongoing work will assess extrasynaptic inhibition, pharmacological modulation of  $\alpha 5$ GABA<sub>A</sub>Rs, and identify potential soluble factors driving the observed changes. Given the prevalence of PNDs and the lack of effective pharmacological interventions, our findings highlight  $\alpha 5$ GABA<sub>A</sub>Rs as a potential target for improving postoperative cognitive outcomes.

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## **Poster**

### **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR203.02/B29

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

**Support:** NSF Cooperative Agreement No. OIA-2242771  
NASA West Virginia Space Grant Consortium, NASA Agreement #  
80NSSC25M7079  
Marshall University Creative Discovery Spring 2025 Award

**Title:** Oral silver nanoparticle exposure disrupts postsynaptic protein organization in the rat hippocampus

**Authors:** \*A. BORA, R. SMITH, E. WILLIAMS, N. SPITZER;  
Biol. Sci., Marshall Univ., Huntington, WV

**Abstract:** Silver nanoparticles (AgNPs) are commonly incorporated in medicinal and consumer products for their antimicrobial properties. AgNPs are shed into the environment during manufacturing and use, and enter the body orally, dermally, or through inhalation. Once inside, AgNPs cross the blood-brain barrier and accumulate in the brain without clearance. Previously, we found that AgNP exposure dysregulates f-actin structure in cultured neural cells. The actin cytoskeleton is critical in maintaining the shape of synapses and organizing neurotransmitter vesicles and receptors. In this study, we sought to determine if oral AgNP exposure disrupts synapses in the hippocampus and striatum of Sprague-Dawley rats. We treated rats with 0 mg/kg (control), 25 mg/kg (low), or 100 mg/kg (high) of AgNPs in 10% sucrose for nine consecutive weekdays. These doses were chosen because they result in brain silver levels that mirror the concentrations estimated to accumulate in the human brain from long-term environmental exposure to AgNPs. After treatment, the brains of half of the rats were collected immediately, while the remaining animals were given a month without AgNP exposure to determine if the bioaccumulation of AgNPs has sustained effects on synapses. Immunohistochemistry was performed on brain sections using the presynaptic and postsynaptic terminal markers vesicular glutamate transporter (VGLUT) and postsynaptic density protein 95 (PSD-95) to label excitatory synapses. Inhibitory synapses were labeled with presynaptic vesicular GABA transporter (VGAT) and postsynaptic gephyrin. Puncta were identified and colocalization of the pre- and post-synaptic terminal markers was quantified using the SynBot plugin for Fiji. We found that PSD-95 puncta and their synaptic colocalization with VGLUT puncta were decreased in the hippocampus of rat brains collected immediately after exposure to AgNPs. Conversely, after a month of exposure to bioaccumulated AgNPs, PSD-95 was overexpressed in the hippocampus, and colocalization with VGLUT puncta increased. Similarly, the number of postsynaptic gephyrin puncta and their colocalization with VGAT decreased in brains collected immediately after AgNP exposure but increased after exposure to bioaccumulated AgNPs. Comparable changes in expression of these excitatory and inhibitory markers were observed in the striatum. The data suggest that oral AgNP exposure alters the number of functional excitatory and inhibitory synapses in the rat hippocampus due to a disruption in postsynaptic proteins. These findings could inform policy on regulating AgNP incorporation in products.

**Disclosures:** A. Bora: None. R. Smith: None. E. Williams: None. N. Spitzer: None.

## **Poster**

### **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.03/B30

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

**Support:** JST SPRING, Grant JPMJSP2108  
Grant in Aid for Scientific Research (B), Grant 25K02374  
JST PRESTO, Grant JPMJPR21E7

**Title:** Systematic analysis of synaptic molecular alterations in the brain caused by several chronic stresses

**Authors:** \*Q. YANG, J. IKEDA, K. NODA, H. SHIMONO, H. SAKAMOTO, K. HIROSE;  
Dept. of Pharmacol., The Univ. of Tokyo, Tokyo, Japan

**Abstract:** Chronic stress has been reported to induce changes in synaptic transmission in several brain regions. However, the molecular mechanisms at the synaptic level underlying these changes remain unclear. To address this issue, we generated three types of stress model mice: a restraint stress model (RES mice), a social isolation stress model (ISO mice), and a chronic corticosterone administration model (CORT mice). We then systematically analyzed the expression of postsynaptic proteins in the brain using quantitative immunofluorescence imaging techniques. In total, we examined ten postsynaptic proteins, including postsynaptic density (PSD) scaffold proteins and glutamate receptors, across five brain regions, including the hippocampus and cerebellum. The results revealed brain region- and stress model-specific alterations in the expression of postsynaptic proteins. In CORT mice, the expression levels of two scaffold proteins, Shank and Homer1, decreased in the molecular layer of the dentate gyrus in both the dorsal and ventral hippocampus. In ISO mice, another scaffold protein, SAPAP, exhibited a distinct alteration: in the molecular layer of the ventral dentate gyrus, its distribution across sublayers was altered, with a relative decrease in the middle layer. Outside the hippocampus, CORT mice showed a decrease in the expression of AMPA-type glutamate receptors in the molecular layer of the cerebellum, whereas no such change was observed in RES mice. These findings indicate that chronic stress induces region- and model-specific alterations in the expression and spatial organization of glutamatergic synaptic proteins, highlighting the diversity of stress effects at the synapse level and providing important insights into the pathophysiology of depression and anxiety disorders.

**Disclosures:** Q. Yang: None. J. Ikeda: None. K. Noda: None. H. Shimono: None. H. Sakamoto: None. K. Hirose: None.

## **Poster**

### **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.04/B31

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

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

**Title:** Compound spines in CA1 pyramidal neurons support spatial navigation.

**Authors:** \*D. CHAUHAN<sup>1</sup>, S. NADKARNI<sup>2</sup>;

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**Abstract:** CA1 pyramidal neurons (PNs) predominantly display place fields, relevant for spatial navigation, and integrate input from CA3 and the entorhinal cortex (EC). Their synapses convert presynaptic electrical signals into chemical signals, driving local plasticity and dendrite-wide coordination that support place field formation. While most hippocampal synapses are simple spine-bouton pairs (simple synapses), recent evidence reveals abundant spine clusters in CA1 PNs innervated by a common bouton/axon. These compound spines (CSs) are especially dense on distal apical dendrites of CA1 PNs and likely targeted by EC's projections—the locus of spatial information. CS's abundance and placement necessitate understanding their electrochemical signalling properties and their influence on the dendritic computation of spatial navigation. To this end, we have developed a morphologically realistic, biophysically detailed multiscale model of CA1 PN with CSs and simple spines (SSs) that provides quantitative insight into the electrochemical signalling. With this model, we investigate the functional advantages of seemingly redundant CS design, in which multiple spines receive identical presynaptic input. We show CSs have a higher probability of N-methyl-D-aspartate receptor-driven  $\text{Ca}^{2+}$  current, which has strong implications for long-term plasticity. Simulating theta-burst stimulus (TBS) in the distal CSs induces stronger  $\text{Ca}^{2+}$  transients in the parent shaft compared to SS. Consequently, we observe a higher propensity of dendritic spikes, which is crucial for overcoming the attenuation and causing depolarisation of the soma. Building on these findings, we tested how CSs affect the temporal and spatial integration of natural activity across the dendritic arbour. Stimulating distal CSs alone, but not SSs, with a TBS transiently increases the  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (CaMKII) activation rate in proximal SS. This suggests that sustained activation of distal CSs can lower the global plasticity threshold. Empirical evidence causally links dendritic plateau potentials to the induction of place fields. Consistent with this, our results show that co-stimulating distal CSs with a proximal SS promotes dendritic plateau potentials and elevates CaMKII activation, both of which have been causally linked with behavioural time-scale plasticity (BTSP), the cellular mechanism driving place field formation. We conclude that the CS designs enable the reliable storage of spatial information and increase transmission efficiency. Additionally, our simulation shows the relevance of CS to BTSP and, therefore, induction of the place field.

**Disclosures:** D. Chauhan: None. S. Nadkarni: None.

## **Poster**

### **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.05/B32

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

**Support:** BBRF Young Investigator Award 32272

**Title:** Nanoscale Analysis of Evoked and Spontaneous NMDAR-Mediated Calcium Signals at Individual Hippocampal Synapses

**Authors:** \*C. I. MCCARTHY, E. T. KAVALALI;  
Pharmacol., Vanderbilt Univ., Nashville, TN

**Abstract:** Neurons in the mammalian central nervous system exhibit both action potential (AP)-synchronized evoked neurotransmission and stochastic spontaneous neurotransmitter release. How postsynaptic neurons distinguish these two modes of transmission and differentially engage downstream signaling pathways remains an open question. Recent evidence from mammalian synapses suggests that spontaneous and evoked glutamate release are spatially and functionally segregated in presynaptic terminals. Our lab previously showed that in rat hippocampal neurons, although evoked and spontaneous NMDA receptor (NMDAR)-mediated calcium transients can co-occur at the same synapse, they show minimal correlation or crosstalk. Moreover, the activation of NMDAR triggers ryanodine receptor-dependent calcium-induced calcium release from the endoplasmic reticulum. In the present study, we investigated the sub-synaptic localization of spontaneous and evoked NMDAR-mediated calcium signals. We performed live-cell imaging using the soluble calcium indicator GCaMP8s in dissociated rat hippocampal neurons, in the presence of AMPAR blockers to isolate NMDAR activity. We detected the local fluorescence maxima regions of interest that functionally correspond to single synapses. Using Thunderstorm deconvolution analysis, we estimated the sub-pixel nanoscale localization of calcium events, conducted cluster and nearest-neighbor analysis. Our results show that spontaneous and evoked NMDAR-driven calcium signals are spatially segregated within individual synapses, with a slight overlap between these populations. These findings support a model in which spontaneous and evoked NMDAR activity engage separate nanodomains, enabling distinct forms of synaptic signaling and plasticity to coexist at the single-synapse level.

**Disclosures:** C.I. McCarthy: None. E.T. Kavalali: None.

## **Poster**

### **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.06/B33

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

**Support:** NIH grant NS089578  
NIH grant NS125782

**Title:** The role of a Par3-PSD95 interaction in postsynaptic compartmentalization

**Authors:** \*M. SALAMEH<sup>1</sup>, H. CAIOLA<sup>2</sup>, M. DENG<sup>3</sup>, P. TORRES<sup>2</sup>, Z. SHI<sup>4</sup>, H. ZHANG<sup>5</sup>;  
<sup>2</sup>Neurosci. and Cell Biol., <sup>1</sup>Rutgers RWJMS, Piscataway, NJ; <sup>3</sup>Dept. of Chem. and Chem. Biol.,  
<sup>5</sup>Neurosci. and Cell Biol., <sup>4</sup>Rutgers Univ., Piscataway, NJ

**Abstract:** Synaptic dysfunction and dendritic spine abnormalities often underlie the cognitive symptoms of neurodevelopmental disorders. Within the dendritic spine, synaptic proteins such as receptors, signaling molecules, and scaffolding proteins are organized into sub-compartments



called nanomodules. Previous studies have found that the number of nanomodules increases in proportion to synaptic strength and spine size, with immature spines having fewer nanomodules compared to mature spines. Nevertheless, the molecular players driving the formation of nanomodules in the synapse are not fully characterized. The scaffolding protein Partitioning Defective 3 (Par3) is known to promote subcellular compartmentalization. Furthermore, recent work in our lab has found that loss of Par3 in mice results in an increased pool of immature dendritic spines. Therefore, we hypothesize that Par3 may promote dendritic spine maturation and stability by driving the formation of nanomodules within the postsynaptic density. Unexpectedly, we discovered that Par3 interacts with PSD95, a key postsynaptic scaffolding protein. We have narrowed this interaction down to be between the C-terminal 4N2 domain of Par3 and the N-terminus of PSD95. Moreover, Par3 colocalizes with and promotes the clustering of PSD95 in heterologous cells. Within these clusters, Par3 exhibits higher mobility than PSD95, and co-expression of Par3 and PSD95 results in reduced Par3 mobility. Currently, we are working to further characterize the Par3-PSD95 interaction by exploring whether this interaction relies on phase separation, a common mechanism for subcellular compartmentalization of proteins. Furthermore, we are examining the biophysical properties of Par3 and PSD95 condensates using micropipette aspiration and whole-cell patch clamp (MAPAC) and investigating the role of Par3 in regulating nanomodule formation at the synapse using super-resolution microscopy.

**Disclosures:** M. Salameh: None. H. Caiola: None. M. Deng: None. P. Torres: None. Z. Shi: None. H. Zhang: None.

## **Poster**

### **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.07/B34

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

**Support:** JST SPRING, Grant JPMJSP2108.  
Grant in Aid for Scientific Research (B), 25K02374  
JST PRESTO, JPMJPR21E7

**Title:** Nanoscale reorganization of postsynaptic density proteins in the dentate gyrus of a corticosterone-induced mouse model of depression

**Authors:** \*J. IKEDA, K. NODA, H. SHIMONO, Q. YANG, H. SAKAMOTO, K. HIROSE;  
Dept. of Pharmacol., The Univ. of Tokyo, Tokyo, Japan

**Abstract:** Chronic stress exposure in rodents induces depression-like behavior and abnormal synaptic transmission in various brain regions, including the hippocampus. However, the molecular mechanisms underlying synaptic alterations in depression remain poorly understood. In this study, we employed quantitative immunofluorescence histochemistry combined with

super-resolution microscopy to examine the postsynaptic density (PSD) scaffold proteins at sub-synapse resolution in the hippocampus of corticosterone-induced depression model mice. These scaffold proteins are essential for anchoring receptors and regulating the efficacy of synaptic transmission. Super-resolution imaging revealed that two PSD protein families, Shank and Homer1, form nanoscale clusters on synapses in the molecular layer of the dentate gyrus (DG). We found a marked decrease in the fluorescence intensity of these PSD scaffold protein clusters, more prominent in the middle molecular layer (MML) than in the outer molecular layer (OML), while their number and area remained unchanged. In addition, the intensity of the metabotropic glutamate receptor subunit mGluR5 was also reduced in the molecular layer of the DG, particularly in the perisynaptic region. Importantly, the severity of depression-like behavior strongly correlated with the regional expression ratio of the scaffold proteins between MML and OML. Our findings suggest that layer-specific nanoscale reorganization of PSDs in hippocampal DG synapses may underlie depression-like behavioral abnormalities, by altering the input balance between MML and OML, which are innervated by the medial and lateral entorhinal cortex, respectively.

**Disclosures:** J. Ikeda: None. K. Noda: None. H. Shimono: None. Q. Yang: None. H. Sakamoto: None. K. Hirose: None.

## **Poster**

### **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.08/B35

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

**Support:** ORED Proof of Concept Funds, UC Merced

**Title:** Tat and other arginine-rich peptides attenuate neuronal activity-induced signaling and gene transcription via extracellular multivalent interactions with NMDA receptors

**Authors:** \*R. N. SAHA;  
Univ. of California, Merced, Merced, CA

**Abstract:** Unlike most peptidic moieties, arginine-rich cationic peptides can penetrate the cell membrane. They are therefore widely used in many cell types, including neurons, to deliver peptide inhibitors in physiological and disease contexts. It is postulated that cationic peptides permeate the cell either via direct penetration or by endocytosis and endosomal release. Unexpectedly however, we discovered that under resting conditions, Tat and other cationic peptides manifest their inhibitory effects in neurons via extracellular mechanisms. These peptides interact with negatively charged extracellular domains of NMDA receptors on neuronal cell surface and inhibit downstream signaling. Such extracellular peptide-receptor contacts are mediated by electrostatic and other non-specific interactions where the like-charge guanidinium pair in arginine plays an obligatory role. Lastly, intracellular delivery of these peptides is

nonetheless possible by hyperpolarizing neurons in tandem with peptide administration. Taken together, we present a new mechanism of cationic peptide activity in neurons, which will allow us to revise and refine their usage in experimental and therapeutic contexts.

**Disclosures:** R.N. Saha: None.

**Poster**

**PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.09/B36

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

**Support:** FONDECYT 11230291  
Programa PIA UC  
FONDEQUIP EQM240080

**Title:** Spine apparatus as a modulator of electrical integration in cortical synapses

**Authors:** \*V. H. CORNEJO;  
Pontificia Univ. Catolica de Chile, Santiago, Chile

**Abstract:** Dendritic spines are specialized postsynaptic compartments essential for communication in the central nervous system. Spines act as biochemical insulators, integrating and compartmentalizing postsynaptic signals, while also serving as electrical compartments. This electrical isolation has been attributed to spine morphology, characterized by a small head and narrow neck, but may also involve their organelle content. One candidate is the spine apparatus, a specialized domain of the smooth endoplasmic reticulum that extends from the dendrite into the neck of a subset of spines. Although its molecular composition is starting to be characterized, the protein synaptopodin is a known marker of this organelle. To investigate the role of the spine apparatus in voltage compartmentalization, we developed in vivo-compatible probes targeting synaptopodin and combined them with optogenetic stimulation and voltage imaging. These constructs were introduced via in utero electroporation in CD1 mice, enabling expression in layer 2/3 pyramidal neurons of the somatosensory cortex. In adult animals, two-photon voltage imaging was performed in vivo, followed by high-resolution confocal microscopy to validate probe expression and subcellular localization. We observed that the number of spines containing a spine apparatus was higher than previously reported in other brain regions. Moreover, voltage recordings revealed that spines containing the spine apparatus exhibited enhanced signal amplification compared to neighboring spines lacking this organelle. These findings suggest that the spine apparatus contributes to the electrical properties of dendritic spines and may play a role in modulating synaptic integration and plasticity in vivo.

**Disclosures:** V.H. Cornejo: None.

**Poster**

## **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.10/B37

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

**Support:** Graduate Program for Medical Innovation, Kyoto University  
MEXT, Japan JP18H05434, JP20K214, JP22K2135362, JP22K18372  
JST CREST JPMJCR20E4  
JST FOREST JPMJFR2141

**Title:** Camkii drives synaptic maturation by coordinating spine remodeling and receptor segregation via liquid-liquid phase separation

**Authors:** \*L. KUO<sup>1</sup>, P.-W. LIU<sup>1</sup>, M. ARIZONO<sup>2</sup>, Y. HAYASHI<sup>1</sup>;  
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**Abstract:** A hallmark of mature excitatory synapses is their localization on dendritic spines, which increase in number and enlarge during development. In addition, recent super-resolution studies have uncovered another key feature of mature synapses—an intricate synaptic nano-architecture. Trans-synaptic nanocolumns, which align AMPA-type glutamate receptor (AMPA) nanodomains with presynaptic release sites, ensure efficient synaptic transmission as neurons mature. However, the mechanism by which these key features of synaptic maturation emerge remains unclear. Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII) is a signaling molecule implicated in regulating excitatory synaptic transmission. Recent findings show CaMKII, beyond its function as a kinase, serves as a structural element through its ability to undergo liquid-liquid phase separation (LLPS). In *in vitro* settings, upon activation, it segregates AMPAR from NMDA-type glutamate receptors (NMDAR) thereby forming biphasic condensates. Given that CaMKII expression increases during development, we hypothesized that it serves as the driving force behind synaptic maturation. Using super-resolution microscopy, we found that immature neurons, which express lower levels of CaMKII, exhibit smaller dendritic spine density and size, as well as less-developed AMPAR and NMDAR nanodomain segregation compared to mature neurons. Remarkably, overexpressing CaMKII in immature neurons was sufficient to recapitulate the features of mature synapses, by increasing spine density and size, and receptor nanodomain segregation. Conversely, a single CaMKII mutation (I205K), which prevents LLPS, abolished these effects. Our findings support the idea that CaMKII-mediated LLPS is the driving force shaping the mature synaptic landscape, suggesting a previously overlooked mechanistic link between dendritic spine formation, enlargement, and receptor nanodomain organization.

**Disclosures:** L. Kuo: None. P. Liu: None. M. Arizono: None. Y. Hayashi: None.

### **Poster**

## **PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.11/B38

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

**Support:** RTG2550/1736 project ID 411422114  
StruBiTEM facility (Cologne, funded by DFG Grant INST 216/949-1 FUGG)  
RRZK computing infrastructure CHEOPS (Cologne, funded by DFG Grant INST 216/512/1 FUGG)

**Title:** Multimodal binding of collybistin controls gephyrin filament formation in synaptic clustering

**Authors:** \*N. BURDINA, F. LIEBSCH, A. MACHA, E. BEHRMANN, G. SCHWARZ;  
Univ. of Cologne, Cologne, Germany

**Abstract:** The multifunctional protein gephyrin clusters glycine and GABA type A receptors at inhibitory postsynapses by oligomerization of its G- and E-domain. Collybistin, a gephyrin-interacting nucleotide exchange factor, mediates gephyrin recruitment and clustering at specific GABAergic postsynapses via phosphoinositide interaction. However, the molecular mechanisms underlying collybistin-dependent gephyrin clustering have remained poorly understood. Using single-particle cryo-electron microscopy we uncovered the structural basis of collybistin-regulated gephyrin clustering, revealing that collybistin controls gephyrin oligomerization into E-domain dimerization-dependent filaments in a lipid-dependent manner: While collybistin alone inhibited filament formation, the presence of plasma membrane phosphoinositides resulted in the assembly of stable gephyrin-collybistin complexes that underwent filament formation. Within these complexes, collybistin binds at distinct positions, with different stoichiometries and conformations, either enhancing or restricting filament assembly and thereby regulating filament formation and elongation. Specifically, plasma membrane-resident phosphoinositides facilitated gephyrin-collybistin complex formation, demonstrating their critical role in membrane targeting and stabilization of gephyrin-collybistin clusters at postsynaptic sites. Disruption of the gephyrin-collybistin complex formation upon phosphorylation of gephyrin at Ser325 resulted in impaired postsynaptic clustering at GABAergic synapses. Collectively, these findings highlight the critical role of gephyrin E-domain dimerization-dependent filament formation for postsynaptic clustering and demonstrate its tight regulation by collybistin, driving specific oligomerization at phosphoinositide-enriched GABAergic synapses.

**Disclosures:** N. Burdina: None. F. Liebsch: None. A. Macha: None. E. Behrmann: None. G. Schwarz: None.

**Poster**

**PSTR203: Postsynaptic Organization and Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR203.12/B39

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

**Support:** R35 ES031686  
P30 ES017885

**Title:** Nmda receptor localization alterations resulting from low-dose, early developmental lead (Pb) exposure in excitatory hiPSC-neurons

**Authors:** \*J. S. SMITH<sup>1</sup>, K. P. DEAN<sup>2</sup>, P. M. JENKINS<sup>3</sup>, J. A. COLACINO<sup>1</sup>, D. C. DOLINOY<sup>1</sup>;

<sup>1</sup>Envrn. Hlth. Sci., Univ. of Michigan Sch. of Publ. Hlth., Ann Arbor, MI; <sup>2</sup>Cell and Mol. Biol., Univ. of Michigan Med. Sch., Ann Arbor, MI; <sup>3</sup>Dept. of Pharmacology, Dept. of Psychiatry, Univ. of Michigan Med. Sch., Ann Arbor, MI

**Abstract:** Developmental lead (Pb) exposure remains a major public health concern due to its lasting impact on brain function through disrupted excitatory neurotransmission—a feature commonly shared by many neuropsychiatric disorders. The CDC's blood lead reference level is 3.5 µg/dL, a threshold exceeded by 2.5% of U.S. children. Excitatory neurotransmission is heavily regulated by N-methyl-D-aspartate receptor (NMDAr) synaptic localization and composition. Previous research has indicated an increase in synaptic NMDAr resulting from early developmental exposure of 1 µM Pb in hippocampal rat cultures (Neal et al., 2010). However, the impact of Pb exposure on NMDAr localization in human-neuronal synapses resulting from lower dose Pb exposure is unknown. This study examines how developmental Pb exposure affects NMDAr localization in human-induced pluripotent stem cell (hiPSC) derived excitatory neurons. Neurotypical patient-derived hiPSCs were differentiated into excitatory neurons via NGN2 overexpression and co-cultured with rat astrocytes. Cells were exposed to 0, 0.16, or 0.625 µM Pb via culture media from DIV8-DIV28, corresponding to approximately 0, 3.32, and 12.95 µg/dL, respectively. Neurons were stained for axon initial segment marker (ankyrin-G), post-synaptic density protein (PSD95), obligatory NMDAr subunit (NR1), and dendritic marker (MAP2), and imaged via confocal microscopy (n = 3 per condition). IMARIS was used to quantify NR1 colocalization with PSD95. Synaptic NMDAr were calculated as the proportion of NR1-PSD95 colocalized spots relative to total NR1 puncta, and analyzed using two-way ANOVA with Tukey's multiple comparisons. NR1 colocalization with PSD95 was significantly increased following exposure to 0.16 µM Pb relative to control (p = 0.0084). No significant differences were observed between 0.625 µM Pb and control (p = 0.473), or in NR1 and PSD95 values relative to MAP2 at 0.16 µM (p = 0.213, 0.205) or 0.625 µM (p = 0.425, 0.930). To our knowledge, this is the first study examining the impact of Pb exposure on NMDAr synaptic localization in human neurons. Preliminary results show that low-dose Pb exposure increases synaptic NMDAr localization in excitatory neurons, which returns to control levels above 0.16 µM—indicating effects at concentrations below both current public health thresholds and those observed in previous research. Further research is in progress to explore how Pb exposure affects NMDAr subunit composition and associated epigenetic mechanisms. This work contributes to understanding the relationship between developmental Pb exposure in excitatory synapses and potential compensatory mechanisms.

**Disclosures:** J.S. Smith: None. K.P. Dean: None. P.M. Jenkins: None. J.A. Colacino: None. D.C. Dolinoy: None.

**Poster**

**PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.01/Web Only

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

**Support:** MEXT; 21H01352  
MEXT; 23K18493

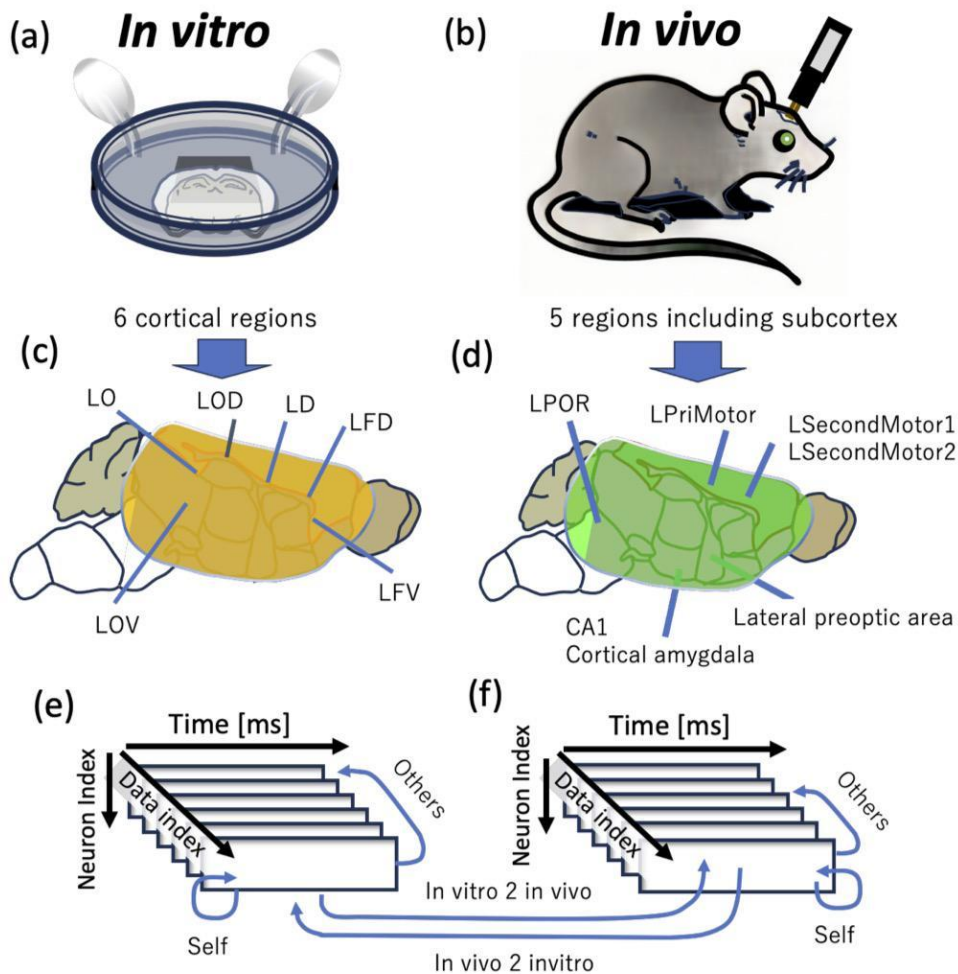
**Title:** Ai bridging in vitro and in vivo neural spike data

**Authors:** \*M. SHIMONO;  
Keio Univ., Tokyo, Japan

**Abstract:** ♦ **Introduction:** Information in the brain is carried by all-or-none spikes, yet forecasting population-level firing patterns remains difficult. A gap separates *in vitro* and *in vivo* studies: results from dish preparations seldom translate to behaving animals. Closing this divide would speed discovery and enable more ethical, efficient work. ♦ **Methods:** Building on prior work [Shimono 2025], we created a bidirectional machine-learning framework that **generates** neural activity across experimental contexts. One network, trained on *in vitro* recordings, predicts *in vivo* spikes ; its twin learns the reverse mapping (Fig. 1). Both employ deep spatiotemporal networks tuned for long-range correlations and diverse firing statistics. Full methodological details appear in Shimono 2025—see <https://arxiv.org/abs/2503.20841>. ♦ **Results & Discussion:** The system delivers accurate cross-domain prediction: *in vitro* activity recreates distributed *in vivo* patterns, and *in vivo* data regenerate dish recordings. A subset of regions acts as “informational hubs,” whose local signals forecast dynamics in distant areas, hinting at a shared computational grammar. :

- **Modeling**—hybrid data enlarge training sets for robust generative models.
- **Design**—hub-centric recording cuts electrode counts yet maintains coverage.
- **Translation**— Use in vitro data to anticipate in vivo outcomes and streamline experimental design.

Our study sets a reproducibility benchmark and traces a direct path from cellular neurophysiology to clinical application. We can share the model trained on data from the informational hub regions—please contact us if interested. ♦ **Author disclosure:** No competing interests.



**Disclosures:** M. Shimon: None.

## Poster

### PSTR204: Cellular Models and Neural Computation

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.02/B40

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

**Title:** Computation with heterogeneous neural substrates

**Authors:** \*R. GAST<sup>1,2</sup>, A. KENNEDY<sup>2</sup>;

<sup>1</sup>Dorris Neurosci. Ctr., Scripps Res., SAN DIEGO, CA; <sup>2</sup>Dorris Neurosci. Ctr., The Scripps Res. Inst., La Jolla, CA



**Abstract:** Neurons are inherently heterogeneous in their structure and electrophysiological response properties. To understand how brain function arises from networks of neurons, we must understand how the heterogeneity of neural tissue relates to that function. In this line of work, we provide novel insight into the computational role of neural heterogeneity by directly relating heterogeneity-induced changes in neural dynamics to changes in neural population function. To this end, we derived a set of mean-field equations for spiking neural networks which allows us to determine a direct relationship between the heterogeneity of spike thresholds and the resulting low-dimensional network dynamics (Gast et al. 2023 PRE). Building on this model, we found that the heterogeneity of inhibitory interneurons plays a crucial role in shaping the dynamic regimes of neural circuits: heterogeneous inhibitory interneuron populations preserve the dynamic repertoire of local excitatory populations, whereas homogeneous interneurons overwrite excitatory dynamic repertoires and facilitate synchronized dynamics (Gast et al. 2024 PNAS). Furthermore, we discovered that neural heterogeneity directly controls the encoding capacity of populations of recurrently coupled excitatory neurons by affecting the multistable dynamic regime of the population. Going beyond our published work, we recently identified distinct roles of synaptic and neural heterogeneity for controlling the dynamical regimes of neural networks (see Fig.1). Using the framework of low-rank RNNs, we discuss how neuromodulatory control of neural vs. synaptic heterogeneity can be leveraged for learning, computation, and task switching.

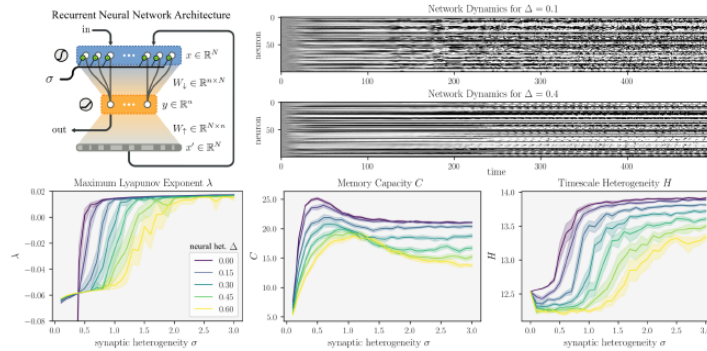


**Figure 1: Differential Effects of Neural vs. Synaptic Heterogeneity on Low-Rank RNNs.** All results were obtained in randomly initialized RNNs ( $N = 2000$  and  $n = 200$ ) subject to white noise input. **Top row:** Exemplary network dynamics were generated for two different levels of neural heterogeneity  $\Delta$ , where neuromodulatory control of synaptic heterogeneity was slowly increased from  $\sigma = 0$  to  $\sigma = 3$ . **Bottom row:** Synaptic heterogeneity acts as the main control parameter to destabilize RNN dynamics and induce a transition to chaotic dynamics. Neural heterogeneity has a stabilizing effect, making the transition to chaos less abrupt. Neural heterogeneity makes the computational capacity of the system more stable to small changes in synaptic heterogeneity, at the cost of a reduction in the overall computational capacity.

**Disclosures:** R. Gast: None. A. Kennedy: None.

**Poster**

**PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.03/B41

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Automated generation of biophysical neuron models using gradient descent based optimization

**Authors:** \*E. WESTEINDE, A. ARKHIPOV;  
Allen Inst., Seattle, WA

**Abstract:** Neurons show a vast diversity in their response properties, overall function, and structure, which has made attaining a general understanding of their capabilities difficult. Biophysical neuron models are a valuable tool to study how a neuron's biological properties give rise to distinct input-output transformations but are notoriously difficult to tune. Here, we use the newly developed tool Jaxley to create a gradient descent-based optimization pipeline to automatically generate biophysical models of neurons. Using morphologies and somatic electrophysiological recordings from the Allen Cell Types Database we develop perisomatic models of single neurons and show that this approach generalizes across cell types and captures individual response properties. This pipeline allows for the systematic generation of such models from large datasets with minimal oversight. Additionally, it simplifies the process of creating complex biophysical neuron models directly from multimodal experimental data and so improves the accessibility of biophysical models as a research technique.

**Disclosures:** E. Westeinde: None. A. Arkhipov: None.

## **Poster**

### **PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.04/B42

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** Kilachand fund-9090014301

**Title:** Simulating Cholinergic Control of Spontaneous Calcium Activity in Layer 5 Pyramidal Neurons

**Authors:** \*D. BALOG<sup>1,2</sup>, H. NGUYEN<sup>3</sup>, D. BOGATOVA<sup>4</sup>, A. DEVOR<sup>2,5</sup>, E. P. STEPHEN<sup>3</sup>;  
<sup>2</sup>Biomed. Engin., <sup>3</sup>Mathematics and Statistics, <sup>4</sup>Biol., <sup>1</sup>Boston Univ., Boston, MA; <sup>5</sup>Dept. of Radiology, Athinoula A. Martinos Ctr. for Biomed. Imaging, Harvard Med. School, Massachusetts Gen. Hosp., Charlestown, MA

**Abstract:** Layer 5 pyramidal cells (L5PCs) are principal projection neurons in the neocortex, integrating synaptic input and coordinating cortical output. Neuromodulators such as acetylcholine (ACh) alter synaptic transmission and neuronal excitability, influencing entire neural networks underlying cognitive function and behavior. Apical dendrites of L5PCs integrate top-down and long-range inputs, however, their spontaneous calcium (Ca) activity and the impact of neuromodulatory inputs are poorly understood *in vivo*. At the mesoscopic scale, cortical Ca signals are typically interpreted as proxies for local population firing rates, despite their relationship being nontrivial. Since ACh modulates Ca spikes, varying cholinergic tone may further complicate the relationship between Ca and spiking activity. Here, we use biophysically detailed compartmental models to study how ACh impacts Ca and

voltage dynamics in L5PCs. The Hay et al. (2011) model of a neuron recreates known *in vitro* behavior of L5PCs, such as generating Ca spikes in response to (1) high-frequency somatic spiking and (2) near-synchronous inputs to the soma and dendrites. We first investigate how neuromodulation impacts these two generative mechanisms, using high-voltage activated Ca conductance channels as a proxy for ACh levels (Dudai et al. 2022). Next, we simulate *in vivo*-like resting state conditions by injecting noisy currents into the soma, dendritic trunk or both. First, our results show that increasing ACh levels lowers the critical frequency of somatic spiking at which Ca spikes occur in the apical tuft. Secondly, increasing ACh decreases the amount of temporal synchrony between somatic and dendritic inputs necessary to generate a calcium spike in a simulated down state, but not an up state. When it comes to the resting state, noisy injected currents produce spontaneous Ca spikes in the apical dendrites through different underlying mechanisms, caused by dendritic stimulation, backpropagating action potentials, or both. We characterize the relationship between Ca spikes and somatic action potentials in these different regimes.

Computational modeling of L5PCs enables scalable, reproducible, and hypothesis-driven exploration of underlying neural mechanisms that are difficult or impossible to detect *in vivo*. Our approach offers a framework to question the impacts of cholinergic modulation on dendritic Ca and intra- and extracellular voltage dynamics. This work contributes to ongoing efforts to bridge local spontaneous dendritic Ca activity in L5PCs to mesoscale cortical dynamics (i.e. widefield Ca and cortical surface electrophysiology) across varying neuromodulatory states.

**Disclosures:** D. Balog: None. H. Nguyen: None. D. Bogatova: None. A. Devor: None. E.P. Stephen: None.

**Poster**

**PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.05/B43

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Modeling astrocytic contributions to Parkinson's disease pathogenesis using three-dimensional human stem cell-derived neuron-astrocyte aggregate cultures

**Authors:** \*W. CHIA, A. SUN;  
Duke-NUS, Singapore, Singapore

**Abstract:** Astrocytes are non-neuronal cells which mediate diverse and essential functions in the central nervous system, such as brain development, homeostasis, and response to insult. Neuroinflammation and astrocyte dysfunction are key characteristics of Parkinson's disease (PD), and astrogliosis is often observed in post-mortem PD brains. However, the role of astrocyte dysfunction in PD pathogenesis remains poorly understood. The study of astrocyte function in PD is hindered by the lack of appropriate human models. The unique characteristics of human astrocytes, coupled with the scarcity of primary human samples,

reinforces the need for human-specific stem cell-derived astrocyte models. In the present study, we utilize a transcription factor overexpression method to induce accelerated differentiation of *FOXA2*-expressing midbrain astrocytes from regionally-patterned neuroprogenitor cells. Additionally, we describe an assembloid model involving the aggregation of induced astrocytes with dopaminergic neurons derived from human midbrain-like organoids. These methods provide a platform by which to study the effects of PD-associated insults on astrocyte physiology and astrocyte-neuron interactions, facilitating a better understanding of astrocytic contributions to disease progression.

**Disclosures:** W. Chia: None. A. Sun: None.

## **Poster**

### **PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.06/B44

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

**Support:** R01MH046742  
R35NS097343

**Title:** The Timescale of Half-(In)activation Alteration Shapes Recovery from Perturbation in a Homeostatic Neuron Model

**Authors:** \*Y. MONDAL<sup>1</sup>, R. L. CALABRESE<sup>3</sup>, E. E. MARDER<sup>2</sup>;

<sup>1</sup>Brandeis Univ., Waltham, MA; <sup>2</sup>Biol., Brandeis Univ., WALTHAM, MA; <sup>3</sup>Biol., Emory Univ., Atlanta, GA

**Abstract:** Neurons maintain activity profiles over their lifetimes, often years, despite facing environmental perturbations. Neurons modulate their activity by altering their channel voltage-dependences but the extent to which they use this to maintain their activity profile is an open question. Activity-dependent modulation of channel voltage-dependence can occur on fast (e.g., phosphorylation) or slow (e.g., subunit incorporation) timescales. We use a computational of activity-dependent homeostasis to examine how the timescale of voltage-dependence modulation might influence how neurons stabilize their activity during perturbation. We perturbed 20 Hodgkin-Huxley-type neurons by increasing extracellular potassium and monitored their recovery. The homeostatic model adjusted channel densities on a slow time scale only and voltage-dependences at fast or slow time scales to restore activity. Eight of the 20 neurons required voltage-dependence modulation to recover; among them, two only recovered with fast modulation and two only with slow modulation. These results demonstrate that voltage-dependence modulation is essential for recovery in some cases. This suggests a role for gating plasticity in the stabilization of neuronal function.

**Disclosures:** Y. Mondal: None. R.L. Calabrese: None. E.E. Marder: None.

**Poster**

**PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.07/B45

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** NSFGRFP

**Title:** Modeling theoretical membrane proteins using a template transporter model

**Authors:** \*B. GIRDLER;  
Univ. of Chicago, Chicago, IL

**Abstract:** Mathematical modeling of ion transporting membrane proteins has provided a way to test mechanistic theories of their individual action. However, researchers are often concerned with systems that are comprised of many types of transporters, some of which are unknown. To address such systems, we propose using a template transporter model that is meant to capture cellular compartment sized phenomenon without the need for the mechanistic understanding or even the identity of each transporter. Previous work has built physical models of specific transporters, such as V-ATPase, and has also created mathematical models of transporters working together, such as modeling the acidification of the lysosome. In the case of lysosomal modeling, early work had trouble identifying the component that limited acidification since CLC, a chloride proton exchanger, was unknown. To address this type of problem, we propose using “theoretical” protein terms for unknown ion relationships that model flux of ions across the membrane by following a simple template transporter model. We show the viability of this method by recreating results from past work that included CLC into its models, and more recent work that identified proton-activated calcium importers at the lysosomal membrane. Though including many “theoretical” protein terms increases the number of parameters of the mathematical model, we show that recent advances in parameter estimation techniques can mitigate the computational burden of fitting these parameters.

**Disclosures:** B. Girdler: None.

**Poster**

**PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.08/B46

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Establishment of an in vitro platform to assess neuronal response to stress across genetic backgrounds

**Authors:** \*C. RODRIGUEZ, M. F. PERA;  
The Jackson Lab., Bar Harbor, ME

**Abstract:** Pluripotent stem cell models enable the study of genetic variation in heterogeneity of biological processes. Such models could be used for the identification of molecular modifiers of neuron aging for protection against age-related neurodegenerative diseases but are currently limited in their capacity to model age in vitro. A potential solution is to use stress response, a process highly interconnected to aging in the brain. While in vivo studies have shown susceptibility to stress predicts overall longevity in mice, this association has yet to be investigated on a cellular level in neurons. To address this, I am developing a high-content in vitro platform for functional assessment of neuronal response to corticosterone, the primary mediator of physiological stress response. This approach enables comparison of stress response across genetic backgrounds as a novel approach to interrogating molecular modifiers of aging vulnerability. I carried out directed differentiation of cortical neurons from two genetically distinct mouse embryonic stem cells lines, C57BL6/J (B6) and WSB/EiJ (WSB). WSB mice exhibit resiliency to age-related phenotypes compared to B6 in vivo. I hypothesize that this will align with strain-dependent effects in cellular response to chronic corticosterone exposure. To ensure responsiveness in my neurons, I exposed them to corticosterone and measured glucocorticoid receptor (GR) nuclear translocation after one hour. I generated an automated imaging and segmentation pipeline that detected GR localization in response to corticosterone exposure. These preliminary experiments have established the technical feasibility and biological relevance of this platform. Ongoing work is now expanding this pipeline for the assessment of downstream corticosterone response through domains of neuronal functions that have been implicated in chronic stress-related decline: cell viability, mitochondrial function, and synaptic signaling. These functional domains are being measured via fluorescent-based probes and live-cell imaging assays. This platform will allow the identification of genetic backgrounds that are susceptible and resilient to chronic stress at a cellular level, providing a foundation to study genetic modifiers of neuronal aging in vitro.

**Disclosures:** C. Rodriguez: None. M.F. Pera: None.

## **Poster**

### **PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.09/B47

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Using iPSC-derived cellular models to model neurological disorders

**Authors:** J. URRESTI, X. KONG, P. MISHRA, D. REQUENA, C. GAO, S. LU, L. CERVANTES-APARICIO, S. ZHANG, \*J. C. SCHEIN, N. LIN;  
iXCells Biotechnologies, San Diego, CA

**Abstract:** During the last decade, induced pluripotent stem cells (iPSCs) have been solidified as a powerful tool for disease modeling. The ability of iPSCs to differentiate into any cell type, such as neurons or glial cells, allows researchers to study disease-relevant cellular phenotypes in a patient-specific context. At iXCells, we have ample experience modeling neurological disorders, such as amyotrophic lateral sclerosis (ALS) or RETT syndrome. These models offer insights into disease mechanisms, enable drug screening, and hold potential for the development of personalized therapeutic strategies. For example, using iPSC-derived motor neurons, the role of stathmin-2 (STMN2) premature polyadenylation in TDP-43 pathogenesis was uncovered in ALS models. In iPSC-derived motor neurons, when TDP-43 or STMN2 were abrogated using CRISPR KO, axon regeneration after taxonomy was inhibited. However, using ASOs to rescue STMN2 or TDP-43 expression, motor neurons recovered the ability to regenerate. In addition, we used iPSC-derived glutamatergic neurons from RETT patients to decipher a neurite outgrowth phenotype; that was later partially rescued using small molecules. A reduction of 20% of neurite outgrowth between RTT and control glutamatergic neurons was observed, and this difference was reduced using Ajmalicine. In summary, our main objective at iXCells is to support the research community by providing affordable and robust iPSC-derived models of disease. We have expertise in neurological and rare disorders, ranging from generating the cell types relevant for each disease to phenotype investigation and using different strategies such as ASO or small molecule screening, to investigate potential therapeutic interventions.

**Disclosures:** J. Urresti: None. X. Kong: None. P. Mishra: None. D. Requena: None. C. Gao: None. S. Lu: None. L. Cervantes-Aparicio: None. S. Zhang: None. J.C. Schein: None. N. Lin: None.

## **Poster**

### **PSTR204: Cellular Models and Neural Computation**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR204.10/B48

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

**Support:** CalciGenix LLC

**Title:** The Excitability Paradox: Modulation of Signal-to-Noise Ratio in CA1 Pyramidal Neurons

**Authors:** \*I. K. MORLEY<sup>1</sup>, B. NATWORA<sup>1</sup>, D. SAFARINI<sup>1</sup>, F. M. MULLER<sup>1</sup>, J. R. MOYER, JR.<sup>1,2</sup>;

<sup>1</sup>Psychological and Brain Sci., <sup>2</sup>Biol. Sci., Univ. of Wisconsin-Milwaukee Grad. Training Program In Neurosci., Milwaukee, WI



**Abstract:** Analogous to the clarity of a radio signal relative to background static, the signal-to-noise ratio (SNR) is a pivotal feature in electrophysiological studies for discerning meaningful neuronal activity from background noise. Previous single-cell measures of SNR utilized mathematical models that assumed uniformity in the family of probability distributions representing neuronal firing across all stimuli. However, emerging evidence suggests that the underlying distribution of neuronal firing shifts in response to the intensity of the current injection, thereby limiting the applicability of these models to a wide variety of stimuli. To circumvent these limitations, we propose the following straightforward and robust measure for single-neuron SNR. When presented with five repetitions of depolarizing current injections ranging from 50 to 500pA (50 pA increments), the signal-to-noise ratio within a single neuron can be defined as the average spike frequency across current injections (the signal) divided by the average standard deviation in spike frequency within current injections (the noise). This ratio is then converted to a logarithmic scale for ease of interpretation. Visually-guided whole-cell recordings (WCRs) were made from CA1 pyramidal neurons within 400  $\mu$ m hippocampal slices maintained at 32 °C in oxygenated aCSF. To test the validity of this SNR metric, SNR was recorded before and after pharmacological administration of either the GABA<sub>A</sub> antagonist bicuculline or the AMPA antagonist CNQX in a within-subjects experimental design. The predictability of SNR changes in response to these pharmacological agents offers insights into the validity of this SNR metric. Preliminary data indicate that SNR significantly decreases following bath administration of 10 $\mu$ M bicuculline (n=6) and increases following bath administration of 15 $\mu$ M CNQX (n=5), validating SNR as a reliable measure of individual neuronal response. Following application of bicuculline, there was a significant increase in mean firing across the input-output curve and a significant increase in intertrial standard deviation in spike frequency. This paradoxical increase in both signal and noise, resulting in a net decrease in SNR, may indicate that small changes in synaptic activity generate significant changes in intertrial standard deviation even within a single neuron. Furthermore, this signal-to-noise ratio measure may have substantial implications for understanding the discriminability of neuronal responses across the input-output curve, as well as the balance between synaptic integration and action potential output in subpopulations of neurons.

**Disclosures:** I.K. Morley: None. B. Natwora: None. D. Safarini: None. F.M. Muller: None. J.R. Moyer, Jr.: None.

## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.01/B49

**Topic:** B.08. Epilepsy

**Support:** NIH/NINDS R01NS115800  
AES post-doctoral fellowship #1066027  
HAWK-IDDRC P50 HD103556

**Title:** Excitotoxic Dendritic Beading During Early Brain Development Impairs Signal Transmission and Synaptic Plasticity

**Authors:** \*P. S. SURYAVANSHI<sup>1</sup>, S. TADINADA<sup>3</sup>, S. BAULE<sup>4</sup>, T. ABEL<sup>5</sup>, J. GLYKYS<sup>2</sup>;  
<sup>1</sup>Pediatrics, The Univ. of Iowa, Iowa city, IA; <sup>2</sup>Pediatrics and Neurol., The Univ. of Iowa, Iowa City, IA; <sup>3</sup>Neurosci. and Pharmacol., Univ. of Iowa, Iowa city, IA; <sup>5</sup>Dept. of Neurosci. and Pharmacol., <sup>4</sup>Univ. of Iowa, Iowa City, IA

**Abstract:** Excitotoxic brain injuries during early brain development lead to cognitive deficits later in life, yet the underlying mechanisms remain unclear. Excessive stimulation of glutamate receptors during excitotoxic insults can produce rapid, varicose swelling of dendrites known as “dendritic beading.” However, the effects on circuit function in the developing brain remain largely unknown. In this study, we evaluated the effects of excitotoxic beading on dendritic morphology (Thy1-H-YFP) and circuit function (Thy1-GCaMP6s) during early brain development (P11-19). We show that brief stimulation of NMDA receptors induced robust and prolonged beading in basal dendrites along with oblique branches and tufts of the apical dendrites in awake, behaving mice and acute brain slices. Dendritic beads were absent in the proximal apical dendrites of hippocampal and cortical neurons, displayed a uniform spatial distribution, and beading was associated with a persistent loss of dendritic spines. Fluorescent calcium imaging revealed that the dendritic beads had persistently high intracellular calcium levels and impeded the propagation of calcium transients along the length of the dendrites. In addition, we evaluated the effect of dendritic beading on hippocampal synaptic plasticity. After NMDA perfusion, hippocampal evoked field potentials were temporarily suppressed, with only ~50% of hippocampal slices showing recovery of responses after 90 minutes. After tetanic stimulation, the NMDA-treated slices that recovered had a reduction in both post-tetanic and long-term potentiation when compared to non-exposed slices. Lastly, we found that clinically relevant hyperosmotic interventions such as mannitol and hypertonic saline effectively resolve excitotoxicity-induced dendritic beads. Additionally, mannitol restored dendritic calcium activity by reducing the proportion of beaded dendrites in the circuits. Our data strongly support that early developmental dendritic beading due to seizures and other related excitotoxic injuries results in circuit dysfunction, which may contribute to cognitive deficits. Hyperosmotic interventions following excitotoxic events during early brain development reduce dendritic beading, enhance dendritic transmission, and may improve cognitive outcomes.

**Disclosures:** P.S. Suryavanshi: None. S. Tadinada: None. S. Baule: None. T. Abel: None. J. Glykys: None.

**Poster**

**PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.02/B50

**Topic:** B.08. Epilepsy

**Support:** NINDS grant R01NS121084  
NINDS grant R01NS124592

**Title:** Weak electric fields modulate epileptiform activity induced synaptic depression in the hippocampus

**Authors:** \*J. ZHOU<sup>1</sup>, L. H. ZUKOWSKI<sup>1</sup>, C.-C. CHIANG<sup>2</sup>, D. M. DURAND<sup>1</sup>;  
<sup>2</sup>Biomed. Engin., <sup>1</sup>Case Western Reserve Univ., Cleveland, OH

**Abstract: Objective:** Patients with epilepsy contend with memory impairment associated with the prevalence of interictal epileptiform discharges (IEDs). IEDs can propagate without synaptic transmission in both in-vivo and in-vitro rodent hippocampi. We focused our investigation on the effects of these non-synaptically propagating IEDs on synaptic plasticity. Specifically, we tested the hypothesis that such IEDs generate long-term depression. **Methods:** IEDs were induced in mouse longitudinal hippocampal slices (i.e., cut along the septotemporal axis of the hippocampus) using 4-aminopyridine (4-AP). Changes in amplitudes and slopes of the population excitatory evoked postsynaptic potentials (pEPSPs) were measured from the CA1 apical dendrite following stimulation at the Schaffer collaterals. Direct current stimulation(DCS) was applied to study the interaction between applied electric fields and IED-induced synaptic plasticity. **Results:** Following long-term potentiation, 4-AP-induced IEDs were observed to propagate along the slice and in the slice generated significant depression as evidenced by a significant decrease in pEPSP slope. Analysis revealed an inverse relationship between IED frequency and synaptic depression magnitude, with lower-frequency IEDs producing more pronounced synaptic downregulation. In addition, anodal DCS effectively canceled the LTD-like effect induced by 4-AP IEDs, restoring synaptic strength. In contrast, cathodal DCS failed to modify or reverse the 4-AP-induced synaptic depression. **Significance:** This study provides insights into how non-synaptic IEDs contribute to synaptic plasticity alterations, offering a potential mechanism for memory impairment in epilepsy. The results highlight the therapeutic potential of anodal DCS for mitigating IED-related cognitive deficits.

**Disclosures:** J. Zhou: A. Employment/Salary (full or part-time): Case Western Reserve University. L.H. Zukowski: None. C. Chiang: A. Employment/Salary (full or part-time): Case Western Reserve University. D.M. Durand: A. Employment/Salary (full or part-time): Case Western Reserve University.

## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.03/B51

**Topic:** B.08. Epilepsy

**Support:** NIH R01NS120945  
R37N119012  
Brain Institute

**Title:** From Metabolite to Modulator: Lactate's role in dentate gyrus function

**Authors:** \*D. GYAMFI;  
Univ. of Virginia, Charlottesville, VA

**Abstract:** Background: Lactate, once viewed solely as a glycolytic byproduct, has emerged as a key player in brain metabolism and signaling. During seizures, increased glycolytic activity leads to accumulation of lactate. In increased glycolysis, pyruvate is formed and converted to lactate through lactate dehydrogenase (LDH). However, recent evidence reveals that lactate also modulates neuronal excitability via HCAR1, a G-protein coupled receptor expressed in the hippocampus, cortex, and cerebellum.

This dual role is especially relevant in epilepsy, where hyperexcitability and metabolic dysregulation coexist. Lactate may exacerbate seizures by fueling hyperactive networks while also downregulating excitability via HCAR1. Timing, concentration, and cellular context of lactate signaling could all influence lactate's role in the brain. It is essential to distinguish to fully understand how lactate shapes neuronal activity.

Given the extensive expression of HCAR1 in the dentate gyrus, we wish to understand its action in the DG. We propose to test the hypothesis that lactate activation of HCAR1 contributes to dentate gyrus gating function.

**Methods:** To test this hypothesis, we used a genetically encoded calcium indicator (GCaMP7) to assess excitability in DGCs from C57Bl/6 mice. Mice were stereotactically injected with a viral mediated mix of GCaMP7 and CaMKII-Cre transgenes to the dorsal and ventral dentate gyrus (DG). Acute hippocampal slices were prepared and calcium fluorescence GCaMP7 expressing DGCs were measured via epifluorescence microscopy. To excite neural networks, potassium concentration in the aCSF was increased from 2 mM (baseline aCSF) to 5 mM (high K<sup>+</sup> aCSF). To study the effect of HCAR1 activation, GCaMP7-expressing DG granule cells were perfused with high K<sup>+</sup> aCSF containing 10 mM L-lactate or high K<sup>+</sup> aCSF containing 100  $\mu$ M 3-chloro-5-hydroxybenzoic acid(3CL-HBA).

**Results:** Preliminary data indicates that lactate increases DGC excitability, contrasting with its inhibitory effects in CA1. In a subset of neurons, we observed rebound excitation during washout, characterized by a transient surge in activity. A similar rebound effect was seen in slices perfused with 3 CL-HBA, HCAR1's agonist. This suggests that lactate-HCAR1 signaling may not only enhance baseline excitability but also prime DGCs for activity-dependent rebound responses.

**Conclusion:** These findings identify the DG as a site of lactate-HCAR1 action. Ongoing and future studies using HCAR1 knockout mice will clarify whether these effects are HCAR1-dependent and their role in seizure susceptibility.

**Disclosures:** D. Gyamfi: None.

**Poster**

**PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.04/B52

**Topic:** B.08. Epilepsy

**Support:** NIH R37NS069861

**Title:** Pathway specific recruitment of dentate gyrus CCK interneurons is compromised after status epilepticus

**Authors:** \*M. AHMADI<sup>1</sup>, V. SANTHAKUMAR<sup>2</sup>;

<sup>1</sup>UCR, Riverside, CA; <sup>2</sup>Mol. Cell and Systems Biol., Univ. of California, Riverside, Riverside, CA

**Abstract:** The hippocampal dentate gyrus (DG) is a critical site for memory processing, integrating object and spatial information from lateral and medial entorhinal cortex (LEC/MEC) respectively. Granule cells (GCs), the principal excitatory output neurons of the DG, exhibit sparse activity largely due to robust feedforward and feedback inhibition mediated by interneurons. Among these, cholecystokinin-expressing interneurons (CCK INs) play a key role in shaping synaptic input and regulating memory encoding. In epilepsy loss of interneurons, results in heightened excitatory activity and aberrant circuit reorganization. However, the mechanisms by which epilepsy alters DG circuitry, particularly with regard to CCK INs, are not fully understood. This study investigates whether CCK IN recruitment and synaptic function are disrupted after status epilepticus (SE). Adult *CCK-Cre* transgenic mice received repeated low-dose kainic acid injections every 20 minutes to achieve Racine stage 4-5 seizures followed by diazepam after 2 hours to model SE. Saline injected controls and post-SE *CCK-Cre* mice received AAV injections to selectively express eGFP in GABAergic CCK INs in the DG and ChR2 in the LEC or MEC projection neurons. Five weeks later, whole-cell recordings were obtained from eGFP expressing CCK INs in acute hippocampal slices. Optically evoked excitatory post synaptic currents (oeEPSCs) were elicited by stimulating ChR2-labeled LEC/MEC axons. In control mice, MEC driven oeEPSC amplitudes were significantly higher than LEC evoked EPSCs (amplitude in pA, LPP:  $0.11 \pm 0.04$  in 15 cells, MPP:  $0.29 \pm 0.07$ , in 14 cells;  $p < 0.01$ , Mann-Whitney test). Notably, CCK INs exhibited pathway specific differences in short-term plasticity with responses to LEC input trains (10Hz) eliciting multi-pulse facilitation while responses to MEC input trains showed multi-pulse depression ( $p < 0.003$ , two-way ANOVA). Following SE, MEC-driven excitation of CCK INs was significantly reduced compared to controls (amplitude in pA, control:  $0.29 \pm 0.07$  in 14 cells, SE:  $0.02 \pm 0.01$ , in 14 cells;  $p < 0.001$ , Mann-Whitney test). Additionally, responses to MEC inputs trains (10 Hz) exhibited greater multi-pulse depression after SE compared to controls ( $p < 0.03$ , two-way ANOVA), suggesting presynaptic dysregulation of MEC inputs after SE. These findings suggest that MEC input to CCK INs might be selectively impaired early after SE, potentially undermining feedback inhibition of the DG circuit and contributing to cognitive dysfunction. Due to their sensitivity to neuromodulators, CCK INs are promising therapeutic targets for restoring inhibition and improving cognitive function.

**Disclosures:** M. Ahmadi: None. V. Santhakumar: None.

## Poster

### PSTR205: Epilepsy Networks and Post-Seizure Modifications

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.05/B53

**Topic:** B.08. Epilepsy

**Support:** NIH-NINDS grant K08NS119800, (J. K. K.)  
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Neurology Foundation/Pediatric Epilepsy Research Foundation Elterman  
Award  
Department of Neurology and Neurological Sciences, Stanford  
NSERC GRANT RGPIN-2017-06662, (J.L.)

**Title:** Seizure-induced myelination of the anterior corpus callosum increases callosal conduction velocity and promotes generalized epilepsy progression.

**Authors:** \*B. PEREZ-RAMIREZ<sup>1</sup>, K. NAIR<sup>2</sup>, K. TAVAKOLI<sup>7</sup>, G. CHAU<sup>3</sup>, M. MCKEAN<sup>8</sup>, V. ALONSO<sup>9</sup>, P. POPSON<sup>2</sup>, J. KIM<sup>4</sup>, J. A. MCNAB<sup>5</sup>, J. CHOI<sup>10</sup>, J. R. HUGUENARD<sup>6</sup>, A. LONGTIN<sup>7</sup>, J. LEFEBVRE<sup>11</sup>, J. K. KNOWLES<sup>12</sup>;

<sup>2</sup>Neurol., <sup>3</sup>Psychiatry and Behavioral Sci., <sup>1</sup>Stanford Univ., Palo Alto, CA; <sup>4</sup>NPIL, Stanford Univ., Stanford, CA; <sup>5</sup>Radiology, Stanford Univ., Palo Alto, CA; <sup>6</sup>Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA; <sup>7</sup>Dept. of Physics, Univ. of Ottawa, Ottawa, ON, Canada; <sup>8</sup>Sch. of Med., Yale, Connecticut, CT; <sup>9</sup>Pharmacol. and Neurosci., Creighton Univ., Omaha, NE; <sup>10</sup>Brain science and Neurol., Ajou Univ. Sch. of Med., Suwon-si, Korea, Republic of; <sup>11</sup>Fundamental Neurobio., Krembil Res. Inst., Toronto, ON, Canada; <sup>12</sup>Neurol., Stanford Univ. Sch. of Med., Palo Alto, CA

**Abstract:** The corpus callosum (CC), the brain's largest commissural white matter tract, synchronizes bilateral seizure activity in generalized epilepsy. We recently demonstrated that seizures induce activity-dependent myelination, leading to increased interhemispheric coherence and progressive seizure burden over time (epilepsy progression) (Knowles et al, 2022). However, it remains unclear whether this myelination is specific to the CC and whether seizure-induced myelination of the CC specifically contributes to epilepsy progression. Using the *Scn8a*<sup>+/-</sup> mouse model of absence epilepsy (Nav1.6 loss of function), we tested whether disrupting CC myelination reduces seizure severity and slows disease progression. First, we determined the extent of seizure-induced myelin plasticity throughout the brain using MRI myelin mapping, by acquiring T1-weighted and magnetization transfer (MT) images; we derived myelin and axon volume fractions and estimated the g-ratio to track CC changes (P21-P51). Next, we genetically blocked activity-regulated myelination by generating *Scn8a*<sup>+/-</sup> mice with tamoxifen-inducible *TrkB* deletion in OPCs (*Scn8a*<sup>+/-</sup>; *TrkB*<sup>fl/fl</sup>; PDGFRα::Cre; OPC *TrkB* cKO; tamoxifen at

P75-77), developing seizures between P90-180. Third, we recorded in vitro compound action potentials (CAPs) from the CC and internal capsule (IC), analyzed callosal conduction velocity (CCV) via custom Python software. Fourth, we induced focal demyelination via stereotactic lysophosphatidylcholine (LPC) injection into the CC at P21, followed by qDTI (P27), MBP labeling (P45), and EEG (P35-41) to assess seizure burden. Fifth, we built a computational thalamocortical model with variable white matter CV based on physiological CC data. MRI showed increased myelination (lower g-ratios) specifically in the anterior CC of *Scn8a*<sup>+/-</sup> mice with seizures. Genetic blockade of activity-dependent myelination reduced interhemispheric hypersynchrony during ictal activity, assessed with EEG coherence. Pathologically increased CCV was found in the anterior CC but not in the IC or posterior CC (outside the seizure network). Genetic blockade of activity-dependent myelination restored CCV to control levels. Preliminary data showed disrupted myelin plasticity (lower fractional anisotropy) and reduced seizure burden in LPC-injected *Scn8a*<sup>+/-</sup> mice compared to controls. The computational model confirmed that increased CCV can promote epilepsy progression. These findings identify seizure-induced myelination in the anterior CC as a key contributor to epilepsy, highlighting a novel target for disease-modifying therapy.

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## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.06/B54

**Topic:** B.08. Epilepsy

**Support:** Epilepsy Foundation  
The American Epilepsy Society  
Brigham Young University

**Title:** Identification of Seizure Cores During the Dynamic Tissue Recruitment into Status Epilepticus

**Authors:** \*M. L. BLOTTER, J. H. NORBY, L. STEPHENS, J. CAHOON, M. SHEPHERD, R. PARRISH;  
Brigham Young Univ., Provo, UT

**Abstract:** Epilepsy affects over 50 million people worldwide, with one-third of patients experiencing seizures that are resistant to medication. One of the most severe seizures is status epilepticus (SE), a prolonged seizure that often becomes pharmacoresistant. SE is a medical emergency which may result in brain damage and has a mortality rate that some studies have

found to be as high as 38%. SE is normally viewed as a brain wide phenomenon that involves the entire telencephalon. However, a true understanding of how SE develops and propagates has been limited by incomplete spatial and temporal resolution. Therefore, we have utilized a micro-electrode array (MEA) to study how SE evolves, allowing unprecedented spatial and temporal detail in a rodent neocortical brain slice model. Preliminary data from our lab suggest that SE does not recruit the brain tissue uniformly but rather follows a modular recruitment pattern, meaning that regions of neocortex can be in SE while other parts of tissue are still experiencing self-limiting seizures. This finding could explain why SE becomes progressively pharmacoresistant in patients and what determines when patients do and do not respond to front line anti-epileptic drugs (AEDs). Furthermore, we find SE to associate with the development of “SE cores”, sites in the tissue where the discharges consistently propagate from. As SE recruits more brain tissue, the number of these cores increases while the spatial identity of early cores remains stable within individual recordings. We are actively exploring factors that may determine what regions become SE cores and why other areas remain penumbral, participating in the SE events but not driving the epileptiform activity. These SE cores suggest potential target areas for AEDs and provide further insights into the temporal dynamics of SE-like activity. In summary, by using the MEA to track local field potential propagation patterns, we are creating a map that clearly characterizes the initiation and spread of SE-like activity in fine detail. Together, these efforts may significantly improve our understanding of SE pathophysiology and support the development of more targeted and effective therapeutic interventions, additional areas we are currently exploring.

**Disclosures:** M.L. Blotter: None. J.H. Norby: None. L. Stephens: None. J. Cahoon: None. M. Shepherd: None. R. Parrish: None.

## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.07/B55

**Topic:** B.08. Epilepsy

**Support:** Brain Research Foundation

**Title:** Seizure Type and Intensity Predict the Recruitment of Spreading Depolarizations

**Authors:** \*K. B. AFRAN-OKESE<sup>1</sup>, J. H. NORBY<sup>1</sup>, D. H. HUMMEL<sup>1</sup>, N. RICKS<sup>1</sup>, J. D. ROLSTON<sup>2</sup>, S. RAHIMPOUR<sup>3</sup>, R. COWAN<sup>3</sup>, E. H. SMITH<sup>3</sup>, R. PARRISH<sup>1</sup>;

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**Abstract:** Spreading depolarizations (SDs) are large waves of neuronal and glial depolarization long suspected to interact with seizures. While past work debated their relevance to human epilepsy, we recently showed that SDs are a prevalent and common feature associating with



seizures in both rodent models and patients with drug-resistant epilepsy (Norby et al., 2025). This study builds on those findings to determine whether specific seizure types and intensities differentially engage SD mechanisms, and to explore the clinical implications of this relationship. In our study, rodent SLEs were recorded in ex vivo brain slices exposed to pro-convulsant conditions using AC/DC electrodes and ion-selective microelectrodes. Human seizures were recorded from patients with drug-resistant epilepsy undergoing pre-surgical monitoring using intracranially implanted macroelectrodes connected to DC amplifiers. Electrodes were localized by coregistering each patient's preoperative MRI with postoperative CT images, and visualization and analysis of the data was performed using custom MATLAB scripts. SDs were observed in ~33% of rodent SLEs and were tightly associated with seizure termination and delayed recurrence. Extracellular potassium ( $[K^+]_o$ ) dynamics did not predict SD induction, while elevated low gamma activity during seizures was a more reliable indicator. In humans, all analyzed seizures exhibited propagating infraslow shifts consistent with SDs. Notably, generalized seizures were more frequently associated with high-amplitude SD-like shifts than focal seizures. Moreover, there was a strong positive correlation between seizure intensity and SD amplitude, suggesting a dose-response relationship between ictal burden and SD recruitment. Importantly, SDs also demonstrated evidence of conserved spatial patterns within individual patients, exhibiting consistent onset zones and regional innervation across multiple seizures. This patient-specific topography parallels the well-established stereotypy of seizure onset and propagation and suggests that SDs may be governed by similar regional susceptibilities within the brain. These findings demonstrate that SDs are not incidental features of seizure activity but instead represent dynamic responses that scale with seizure type and intensity. The dose-dependent nature of this relationship suggests that SDs may be actively recruited by the brain as a self-terminating mechanism during high-intensity seizures. Understanding the mechanisms driving this process could inform new therapeutic strategies for interrupting seizures, especially in cases of prolonged or generalized ictal activity

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## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.08/B56

**Topic:** B.08. Epilepsy

**Support:** NIH-NINDS Grant U01 NS117284

**Title:** Chronic Dysregulation of Fyn-Tau Signaling Following GD Exposure in a Rat Model

**Authors:** \*D. LUO<sup>1</sup>, L. E. MCGEORGE<sup>2</sup>, N. MASSEY<sup>1</sup>, S. SUNDARA VASANTHI<sup>1</sup>, T. THIPPESWAMY<sup>1</sup>;

<sup>1</sup>Biomed. Sci., <sup>2</sup>Iowa State Univ., Ames, IA

**Abstract:** Organophosphate nerve agents (OPNAs) represent a persistent chemical threat due to their acute lethality and poorly understood long-term effects on the brain. Among them, soman (GD) is particularly hazardous due to its rapid and irreversible inhibition of acetylcholinesterase (AChE), swift brain penetration, and resistance to standard oxime-based reactivation once aging occurs. Acute medical countermeasures such as atropine, HI-6, and benzodiazepines provide life-saving cholinergic suppression but fail to prevent chronic neurological sequelae in survivors. To investigate molecular mechanisms underlying GD-induced brain injury, we employed a mixed-sex rat model. Adult Sprague Dawley rats received GD (132 µg/kg, s.c.), followed by immediate administration of atropine (2 mg/kg, i.m.) and HI-6 (125 mg/kg, i.m.). Seizure activity was monitored for an hour, after which midazolam (3 mg/kg, i.m.) was administered. At 12 weeks, a subset of animals was euthanized using pentobarbital sodium (100 mg/kg, i.p.), and fresh brain tissue was collected for downstream analysis. Western blotting and co-immunoprecipitation assays were used to examine protein signaling networks associated with chronic brain injury. We identified sustained dysregulation of the Fyn-Tau signaling axis in brain regions susceptible to GD-induced damage, including altered protein-protein interactions relevant to synaptic stability and glial activation. These results highlight the involvement of Fyn-related pathways in the persistent neuropathology following OPNA exposure. Given the multifactorial nature of OP-induced neurotoxicity, this work supports continued investigation into converging molecular mechanisms that may drive long-term dysfunction and underscores the need for therapeutic strategies targeting the multilayered dysregulation in brain injury.

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## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.09/B57

**Topic:** B.08. Epilepsy

**Support:** National Center for Advancing Translational Sciences  
National Institutes of Health UL1 (# TR001860)  
UC Davis Clinical Translational Science Center (CTSC) KL2 Award (# TR001859)

**Title:** Epilepscope: Personalized Seizure Forecasting for People with Epilepsy

**Authors:** \*Z. MCNAUGHTON<sup>1,2</sup>, K. KIVIAT<sup>2,1</sup>, J. PATEL<sup>2</sup>, C. ARMSTRONG<sup>2,1</sup>, S. TOPRANI<sup>2,1</sup>;  
<sup>1</sup>Neurol., <sup>2</sup>Univ. of California, Davis, Davis, CA

**Abstract:** Epilepsy affects over 50 million people worldwide, with nearly 3.4 million in the United States alone. Epilepsy patients face unpredictable seizures, impacting daily life by limiting activities such as driving, working, and socializing. We are striving to develop noninvasive biomarkers to assess seizure risk, empowering patients to make informed decisions. Identifying low-risk periods allows for normal activities, while high-risk periods could prompt precautionary measures such as avoiding certain activities, using preventive medications, or taking immediate protective actions. However, seizure prediction is highly individualized. Current population-trained detection algorithms lack the precision needed for personalized forecasts. The goal of this project is to identify a high-risk state minutes before a seizure and to distinguish high-risk vs low-risk days, ideally with only the limited data available from commercial neurostimulator devices.

We are using intracranial EEG (iEEG) data collected from depth electrodes implanted in patients undergoing pre-surgical epilepsy monitoring. Electrodes are strategically placed within seizure onset zones (SOZ) and in non-SOZ regions to record electrical activity from adjacent brain tissue. We quantify the effective connectivity of the brain over time by calculating coherence between all pairs of recording channels in physiological frequency bands. Using principal component analysis (PCA) we reduce this data to a low-dimensional state space that can be visualized and classified via logistic regression. We have performed this analysis using recordings from 100+ iEEG contacts. We have also preliminarily applied it a subset of four contacts, either in the SOZ (as captured by closed-loop Responsive Neurostimulation (RNS) devices) or in areas outside the SOZ (as recorded by open-loop Deep Brain Stimulations (DBS) devices).

Analysis of patients (n=11) using all 100+ iEEG contacts has shown that we can distinguish pre-seizure brain states seconds to minutes before a seizure. In preliminary work (n=1), we have found similar results using only four contacts, either in the SOZ or outside of the SOZ. We have also found (n=1) distinct clusters in state space during non-seizure baseline periods on days with many seizures compared to days without seizures.

These results could provide patients early insight on high-risk days and greater predictive power minutes before seizure onset. This would shift epilepsy care from reactive to proactive, improving patient independence and quality of life. It also lays the groundwork for adapting iEEG models to simpler systems like RNS, DBS, or wearables for real-world use.

**Disclosures:** Z. McNaughton: None. K. Kiviat: None. J. Patel: None. C. Armstrong: None. S. Toprani: None.

## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.10/B58

**Topic:** B.08. Epilepsy

**Support:** NSF GRFP  
CURE Epilepsy Taking Flight Award  
NIH NINDS K08 NS121464  
R01HL174547  
Taubman Institute Kenneth Eisenberg Emerging Scholar  
UMMS Research Scouts Award

**Title:** What Makes a "High-risk" *Scn1a*<sup>+/-</sup> Mouse? Linking Seizure Burden, Respiratory Physiology, and Brainstem Networks to Understand SUDEP Risk in Dravet Syndrome

**Authors:** \*K. M. SANTIAGO COLON<sup>1</sup>, N. ELDRUBI<sup>1</sup>, K. ARAKAWA<sup>1</sup>, R. SHEN<sup>2</sup>, Y. DEMETRIOU<sup>1</sup>, X. ZHANG<sup>1</sup>, A. HOLLIER<sup>1</sup>, M. LEE<sup>1</sup>, J. BARDEN<sup>1</sup>, E. S. LEVITT<sup>3</sup>, J. MATTIS<sup>4</sup>;

<sup>2</sup>Neurol., <sup>3</sup>Pharmacol., <sup>1</sup>Univ. of Michigan, Ann Arbor, MI; <sup>4</sup>Univ. of Michigan, Ann Arbor, Ann Arbor, MI

**Abstract:** Sudden Unexpected Death in Epilepsy (SUDEP) is the second leading cause of life years lost to neurological disease. Despite SUDEP's devastating impact, there are currently no biomarkers or preventative treatments. The strongest known risk factor is a history of frequent bilateral tonic-clonic seizures. However, it remains unclear whether this reflects a simple aggregation of fixed per-seizure risk or whether recurrent seizures remodel neuronal circuits - including those regulating respiration - such that per-seizure risk increases. Identifying mechanisms by which seizures increase SUDEP risk may enable targeted interventions to predict or prevent it. We investigated seizure-associated changes in SUDEP risk, respiratory function, and central respiratory circuitry in a mouse model (*Scn1a*<sup>+/-</sup>) of Dravet Syndrome (DS), a severe developmental and epileptic encephalopathy in which SUDEP is the leading cause of death. To isolate genotype versus seizure burden effects, we divided *Scn1a*<sup>+/-</sup> mice into a "high-risk" group, in which we induced repeated seizures (via hyperthermia), and a "low-risk" group, in which we did not. Wild-type (WT) littermates were included for both groups. Outcome measures included (1) spontaneous mortality (presumed SUDEP), (2) interictal/postictal plethysmography, and (3) cFos immunohistochemistry in brain regions regulating respiration and arousal following a final hyperthermia seizure. Plethysmography and immunohistochemistry were performed at a time point when the high-risk group had elevated short-term SUDEP risk. High-risk *Scn1a*<sup>+/-</sup> mice, which underwent repeated hyperthermia seizures on postnatal days (P)19, P21, and P23, showed significantly elevated mortality (50%) by P23 compared to low-risk *Scn1a*<sup>+/-</sup> mice. When tested at P22, *Scn1a*<sup>+/-</sup> mice had altered respiratory parameters postictally, including decreased breathing frequency and prolonged inspiratory and expiratory times compared to WT controls; analyses comparing high- and low-risk *Scn1a*<sup>+/-</sup> mice are ongoing. Immunohistochemistry revealed that high-risk *Scn1a*<sup>+/-</sup> mice had elevated cFos expression across multiple brain regions involved in respiratory control, compared to both WT and low-risk *Scn1a*<sup>+/-</sup> mice. Our findings suggest repeated seizures in *Scn1a*<sup>+/-</sup> mice increase mortality and respond differently to individual seizures compared to low-risk counterparts. Ongoing work will further quantify respiratory and seizure-evoked respiratory circuit activity. Overall, this high-risk/low-risk model enables a mechanistic study of seizure effects on SUDEP risk while controlling for genotype and survivorship bias.

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**Poster**

**PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.11/B59

**Topic:** B.08. Epilepsy

**Support:** NIH R01 NS126594  
Brain Institute

**Title:** Spatial metabolic profiles of brain sections from mouse models of absence epilepsy

**Authors:** \*E. PEREYRA<sup>1</sup>, M. P. BEENHAKKER<sup>2</sup>;  
<sup>2</sup>Pharmacol., <sup>1</sup>Univ. of Virginia, Charlottesville, VA

**Abstract:** Absence epilepsy is characterized by non-convulsant seizures associated with EEG patterns known as spike wave discharges (SWDs). Ethosuximide, the first line treatment for absence epilepsy, fails 50% of patients, thereby motivating the need to identify more effective treatment options. Our lab has observed that shifts in cellular metabolic state and fuel availability exacerbates SWDs. However, the role of neuronal metabolism in SWD generation remains unknown.

To resolve how metabolism regulates SWDs, we seek to establish a comprehensive metabolic profile of neuronal metabolism in the Stargazer mouse, a commonly used rodent model of absence epilepsy. Using MALDI-TOF imaging, we generate spatially resolved mass spectra at defined points throughout whole-brain sections from Stargazer and non-epileptic control mice. Preliminary data demonstrates that MALDI-TOF imaging can resolve metabolite and lipid presence in 50  $\mu$ M pixel regions throughout fresh frozen brain sections of Stargazer mice, thereby providing us with the ability to elucidate differential metabolic pathways among different brain structures and across different mice. This is achieved using Spatial Augmented Multiomics Interface (SAMI), a computational workflow designed for MALDI-TOF imaging analysis. Overall, our study provides a preliminary spatial map of neuronal metabolic features associated with SWDs and serves as a steppingstone to determine if targeting metabolic processes may serve as a treatment option for patients with absence epilepsy.

**Disclosures:** E. Pereyra: None. M.P. Beenhakker: None.

**Poster**

**PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR205.12/B60

**Topic:** B.08. Epilepsy

**Support:** NIH Grant 1R37NS115439

**Title:** Early life seizures induce long lasting transcriptomic changes in a subpopulation of CA1 pyramidal neurons

**Authors:** \*A. CHAVEZ<sup>1</sup>, Y. BAYLEYEN<sup>1</sup>, A. R. WADHWANI<sup>1</sup>, S. DUTKO<sup>1</sup>, A. J. BARBOUR<sup>1</sup>, A. CRISTANCHO<sup>2</sup>, D. M. TALOS<sup>1</sup>, F. E. JENSEN<sup>1</sup>;  
<sup>1</sup>Neurol., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA; <sup>2</sup>Neurol., Children's Hosp. of Philadelphia, Philadelphia, PA

**Abstract:** Early-life seizures (ELS) can cause permanent cognitive deficits and network hyperexcitability. However, cell type-specific molecular mechanisms driving persistent deficits after ELS are unknown. Using mice with targeted recombination of activated populations (TRAP) we genetically labeled neurons activated by kainate-induced (KA) ELS in immature mice at postnatal day (P)10 and shown that the labeled tdTomato-positive (tdT+) CA1 neurons but not surrounding neurons, exhibited persistent increases in AMPA receptor activity with increased inward rectification, downregulation of GluA2 subunit expression, and dysregulated LTP and LTD at P14-16 and in later life at P30-35 (doi: 10.1172/JCI1175167). The present study aimed to determine whether there were long lasting transcriptomic changes in these tdT+ CA1 neurons compared to surrounding tdT- CA1 neurons. Following ELS-TRAP at P10, we used fluorescence-activated cell sorting to separate tdT+ and tdT- cells from micro-dissected hippocampal tissue at P30, followed by single-nucleus RNA-sequencing (snRNA-seq) analysis. Bioinformatic analyses using Seurat and enrichR enabled the identification of cell types, differential gene expression between tdT+ and tdT- CA1 neurons, and comparisons against established gene datasets relevant to synaptic function and neurological disorders. The ELS-TRAPed neurons, marked with tdT as reporter gene under the immediate early gene cFos promoter, expressed a distinct transcriptomic signature compared to tdT- neurons from KA treated mice. We found 206 differentially expressed genes (DEGs) between groups, with 181 genes downregulated and 25 genes upregulated in tdT+ compared to tdT- neurons. Gene ontology analysis of DEGs revealed prominent dysregulation in pathways related to ion channels, synaptic receptors, and plasticity. We also identified a distinct subset of DEGs that have been previously identified as important for synaptic function (n = 35) and related to genetic risk for autism spectrum disorders (n = 23). Consistent with our prior reports, we observed transcriptional downregulation of *GRIA2* (log<sub>2</sub> fold change = -0.171, adjusted P-value = 1.679 e-22). These findings show that enduring transcriptomic modifications occur in ELS-activated CA1 neurons, compared to the surrounding neurons that may mediate the persistent hyperexcitability, cognitive impairment, and synaptic dysplasticity we have previously reported. Future studies using this dataset will enable us to examine potential targetable pathways that may yield novel clinically relevant therapies to prevent long-lasting consequences of ELS.

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## Poster

### PSTR205: Epilepsy Networks and Post-Seizure Modifications

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.13/C1

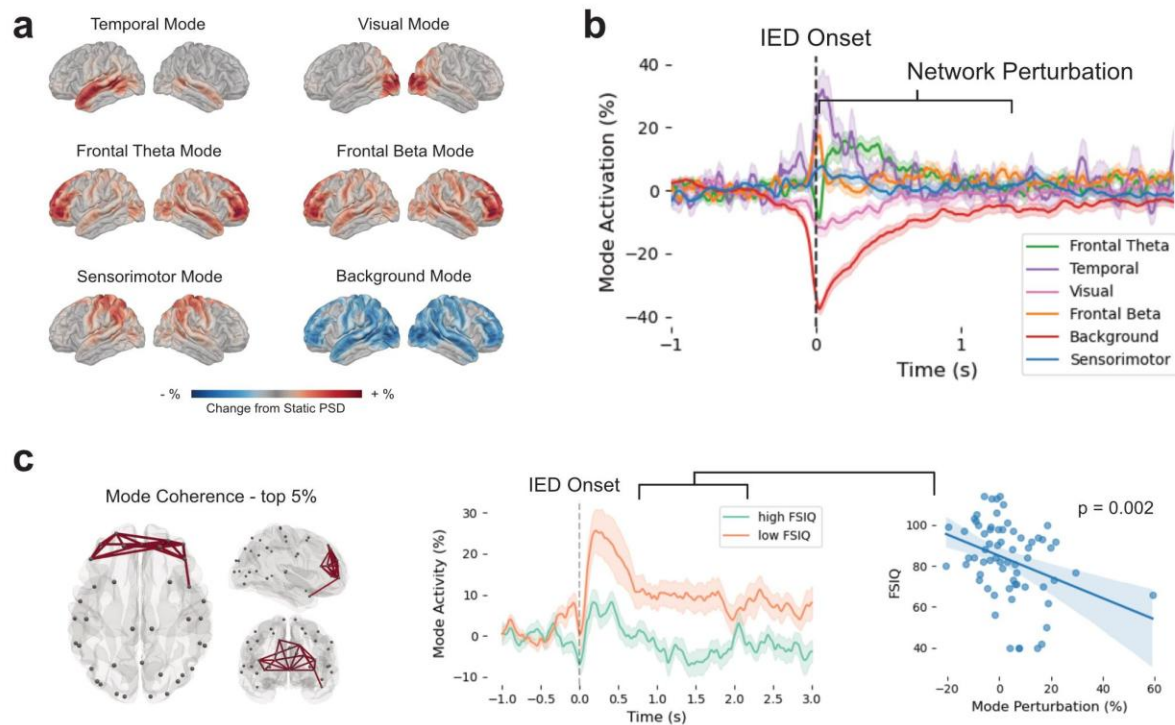
**Topic:** B.08. Epilepsy

**Title:** Dynamic interactions of interictal discharges with resting state networks in children with epilepsy

**Authors:** \*S. C. COLEMAN<sup>1</sup>, K. MITHANI<sup>2</sup>, S. M. WONG<sup>3</sup>, H. SURESH<sup>1</sup>, G. M. IBRAHIM<sup>4</sup>;

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**Abstract:** Epilepsy is the most common serious neurological disorder in children. Affected children often exhibit neurocognitive deficits related to the occurrence of interictal epileptiform discharges (IEDs). Although deleterious interactions between IEDs and intrinsic brain networks have been proposed as a mechanism underlying cognitive impairment in epilepsy, measurement of these transient dynamics remains challenging. In the current work, we used magnetoencephalography (MEG) along with dynamic network models of brain activity to directly investigate disruption of cognitive networks following IEDs in children with epilepsy. Resting-state MEG data were recorded from 67 children with temporal lobe epilepsy at the Hospital for Sick Children (Toronto, Canada). Full-scale intelligence quotient (FSIQ) was measured for each patient as a robust measure of general cognitive ability. MEG data were preprocessed and projected into 38 cortical brain regions using a linearly constrained minimum variance beamformer. Dynamic Network Modes (DyNeMo, osl-dynamics), a self-supervised machine learning approach, was used to infer 6 dynamic networks from the data, each capturing a unique signature of resting-state power and connectivity. The relative change in dynamic mode activity post-IED (0.5s:2s) was taken as a measure of network perturbation, and compared with age-adjusted FSIQ using a linear mixed effects (LME) model. The 6 inferred modes (a) included frontal, temporal, visual and sensorimotor modes. The temporal theta mode exhibited a spike in activity at IED onset but no persisting perturbation, while the frontal theta and visual alpha modes were perturbed for several seconds, reflecting IED-related network disruption (b). Subjects with lower FSIQ exhibited greater post-IED perturbation (c), specifically in the frontal theta mode ( $p = 0.002$ , LME) - a network often associated with higher-order functioning. This work provides mechanistic insight into the relationship between IED-related network disruption and cognitive impairments in epilepsy.



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## Poster

### PSTR205: Epilepsy Networks and Post-Seizure Modifications

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.14/C2

**Topic:** B.08. Epilepsy

**Support:** CNPq Grant 446688/2024-0  
NIH Grant U24EB028998  
NSF Grant 1904444-1042C  
NYS Grant DOH01-C38328GG-3450000

**Title:** New insights of neocortical high-frequency oscillation mechanisms using a large-scale biophysically detailed model

**Authors:** \*F. D. BORGES<sup>1</sup>, J. V. MOREIRA<sup>2</sup>, G. S. VILAR HIGA<sup>3</sup>, S. DURA-BERNAL<sup>2</sup>;  
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**Abstract:** Patients with drug-resistant epilepsy often require surgery to reduce their seizure burden. Implantation of intracranial electrodes is used in planning these surgeries, where electrophysiological biomarkers such as fast ripples (FR), a type of high-frequency oscillation (HFO), are needed to identify the epileptogenic zone. Therefore, a better understanding of the neurophysiological mechanisms responsible for generating this HFO is essential. In this study, we employed a biophysically and anatomically detailed thalamocortical model to simulate intracranial electroencephalography (iEEG) signals. The model incorporates transmembrane currents from morphologically detailed cortical neurons, enabling realistic extracellular potential generation. Simulated iEEG signals exhibited features consistent with human cortical recordings during sleep, including comparable FR rates and spectrogram characteristics. Our results show that FRs emerge at the onset of highly synchronous network events, marked by increased firing rates of excitatory neurons. These events can be spontaneously triggered by deep-layer (L5 or L6) excitatory neurons. During FRs, more than 80% of neurons fire a single spike, while the remaining neurons exhibit inter-spike intervals (ISIs) ranging from 7 to 18 ms—below the FR frequency band. Additionally, some L5/6 excitatory neurons across different morphological classes fire preferentially at the troughs of the iEEG FR oscillation. We further demonstrate that FR rates increase significantly with enhanced excitability of L5 excitatory neurons. In such cases, L5 neurons act as primary initiators of FRs, while feedback from L6 contributes to their maintenance. Our biophysically detailed cortical column model reveals key mechanisms underlying fast ripples (FRs), integrating realistic cell morphologies and synaptic dynamics essential for simulating iEEG signals. By bridging intracellular activity with extracellular recordings, this open-source model links microcircuit dysfunction to clinical biomarkers, offering a valuable tool for epilepsy research and surgical planning.

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## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.15/C3

**Topic:** B.08. Epilepsy

**Support:** NIH R01NS112538  
NIH P01NS127769  
NIH 5R35NS116852

**Title:** Voltage-imaging derived cellular network architecture transiently changes during seizure onset

**Authors:** \*K. P. LILLIS<sup>1</sup>, L. A. LAU<sup>2</sup>, P. O'GORMAN<sup>3</sup>, K. J. STALEY<sup>4</sup>;

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**Abstract:** It is tempting to imagine the brain as a network of neurons with stable synaptic connections that perform a fixed computation (akin to a trained convolutional neural network). However, networks of living neurons constantly vary on timescales ranging from milliseconds to years due to processes such as GABAergic inhibition, short- and long-term synaptic plasticity, changes in intra- and extracellular ion concentrations, and metabolic processes. In some cases, these changes can drastically alter the propagation of signals in the network. For example, the epileptic brain can transiently switch from “normal” function to a state of seizure. The nature of these ictogenic transitions at the cellular level remains largely unknown due to challenges in dynamically mapping connectivity with sufficient spatiotemporal sampling. In this work, we use the mouse organotypic hippocampal slice culture, which develops spontaneous recurrent seizures during the first week in culture and can be imaged in its entirety in a single field of view, to continuously monitor changes in functional network connectivity that emerge during transition to seizure. Specifically, we are using the red-shifted voltage sensitive fluorescent protein Varnam-2 to image voltage at >1kHz simultaneously in hundreds of cells. Functional connectivity is inferred by computing a spike-triggered average network response to action potentials in each cell (i.e. when cell X fires, what is the average response in every other cell?). Since voltage sensors are sensitive to subthreshold depolarization and hyperpolarization, we can image, for the first time, excitatory and inhibitory networks. Here we quantify connectivity in 3 epochs of epileptiform activity: postictal, interictal, and preictal. Preliminary data indicate that, as seizure approaches, excitatory connectivity increases, while inhibitory connectivity decreases. Graph theory-based analyses reveal that mean path length decreases, while clustering and maximum between centrality increase, which suggest the emergence of a small-world network just before transition to frank seizure. Together, these findings support a model where a small population of key neurons transiently serve to pathologically synchronize the network. These “key cells” represent putative therapeutic targets for anti-epileptic interventions.

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## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.16/C4

**Topic:** B.08. Epilepsy

**Support:** NIH Grant 5R01NS122385

**Title:** Role of neuronal STAT3 in modulating intrinsic and synaptic excitability during epileptogenesis

**Authors:** \*G. YAZDANI<sup>1</sup>, D. FONSECA-BARRIENDOS<sup>2</sup>, S. J. RUSSEK<sup>4</sup>, R. BEN-SHALOM<sup>5</sup>, J. A. GRAY<sup>3</sup>, A. BROOKS-KAYAL<sup>6</sup>;

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**Abstract:** Temporal lobe epilepsy (TLE) is characterized by spontaneous seizures, network hyperexcitability, and cognitive impairment. Intra-hippocampal kainic acid (IHKA) induces status epilepticus (SE), initiating molecular cascades that drive epileptogenesis. Signal Transducer and Activator of Transcription 3 (STAT3), a transcription factor activated during SE, mediates inflammatory signaling, neuronal remodeling, and synaptic plasticity. Prior evidence suggests that STAT3 activation promotes seizure progression and persistent excitability changes. To examine STAT3's role in excitatory neurons during epileptogenesis, we used neuronal STAT3 knockout (nSTAT3KO) mice and evaluated their neuronal response to IHKA, building on previous findings that neuronal STAT3 deletion mitigates seizure development and cognitive deficits. Our recordings from dentate granule cells (DGCs) revealed minimal genotype differences 48 hours post-SE; however, at 4 weeks, STAT3KO mice display trends toward normalized intrinsic excitability, consistent with reduced epileptogenic remodeling. To characterize these effects, we will use whole-cell patch-clamp recordings from acute hippocampal slices to assess intrinsic parameters (e.g., resting membrane potential, input resistance, action potential dynamics) and synaptic properties, including miniature excitatory and inhibitory postsynaptic currents (mEPSCs, mIPSCs). Additionally, we will examine network excitability using high-density Multi-Electrode Array (MEA) recordings in IHKA-injected STAT3KO and control slices, analyzing spiking patterns, theta-band oscillations, and circuit synchrony to assess whether STAT3 deletion alters the emergence or propagation of epileptiform activity. We hypothesize that STAT3 deletion reduces intrinsic hyperexcitability and aberrant network activity by modulating synaptic transmission. These studies will clarify how STAT3 influences cellular and network excitability during epileptogenesis and inform strategies for treating epilepsy via anti-inflammatory pathways.

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## **Poster**

### **PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.17/C5

**Topic:** B.08. Epilepsy

**Support:** R01 NS121106  
R01 NS131728

Wu Tsai Neurosciences Institute Postdoctoral Scholars Program – Brain Resilience Track

**Title:** Axo-axonic cell control of the axon initial segment in chronic epilepsy

**Authors:** \*A. M. GOETTEMÖLLER<sup>1</sup>, S. MALHOTRA<sup>1</sup>, P. M. KLEIN<sup>1</sup>, A. LOSONCZY<sup>2</sup>, I. SOLTESZ<sup>1</sup>;

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**Abstract:** Temporal lobe epilepsy (TLE) is the most prevalent form of epilepsy in adults and is frequently resistant to current antiepileptic drugs, which often produce significant side effects. A major obstacle to developing new therapeutic approaches is the limited understanding of the specific cellular and circuit-level mechanisms driving TLE. One key, yet unresolved question concerns the mechanisms underlying excessive and dysregulated action potentials at the axon initial segments (AIS) of excitatory principal cells (PCs), a process thought to be critical in TLE pathophysiology. The AIS receives specialized GABAergic input from axo-axonic cells (AACs), a unique and evolutionarily conserved interneuron subtype that exclusively targets the AIS of PCs. This synaptic arrangement positions AACs to exert powerful control over action potential initiation. However, due to prior technical challenges, the in vivo function and regulation of AACs in both healthy and epileptic hippocampal circuits remain poorly understood. In this project, we leverage recent advances in large-scale, high-resolution in vivo imaging, electrophysiology, optogenetics, and behavioral assays to investigate the role of AACs in a well-established mouse model of chronic TLE—the intrahippocampal kainate model, applied ventrally in CA1. We aim to determine how AAC-mediated GABAergic signaling at the AIS contributes to circuit hyperexcitability and cognitive dysfunction in epilepsy. Specifically, we test whether targeted modulation of AAC activity can attenuate pathological network activity and improve behavioral outcomes. In doing so, we also address longstanding debates about the interneuronal control of the AIS in healthy and epileptic circuits in vivo.

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**Poster**

**PSTR205: Epilepsy Networks and Post-Seizure Modifications**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR205.18/C6

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Antiepileptogenic effect of CDDO-EA via dual modulation of oxidative stress and inflammation in acquired epilepsy

**Authors:** \*Y. SHEENI;

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**Abstract:** Reactive oxygen species (ROS) and oxidative stress have been implicated in the pathophysiology of acquired epilepsy. Activation of the Nrf2 pathway, which regulates genes involved in detoxification, antioxidants, and anti-inflammatory agents, offers a potential strategy to prevent or mitigate the development of epilepsy. Our study aimed to evaluate the antiseizure and antiepileptogenic effects of CDDO-EA, an Nrf2 activator, in several acquired epilepsy models in rats, along with its antioxidant and anti-inflammatory effects. Acute seizures were induced by applying the Pentylentetrazol (PTZ) model to assess the antiseizure effect in rats. Antiepileptic and antiepileptogenic effects were evaluated in the acquired epilepsy model: Kainic Acid-Induced Post-Status Epilepticus (KA-SE) and ECoG recordings were analyzed for each rat. The antioxidant and anti-inflammatory properties of CDDO-EA were determined by standard assays. We have shown that given one hour before PTZ-induced seizure, CDDO-EA prevented the emergence of seizures in 50% of treated animals, delayed seizure onset, reduced seizure duration, and attenuated seizure severity. Biochemical analysis showed a notable reduction in inflammatory cytokines and an increase in post-treatment antioxidant effects. Following KA-SE induction, CDDO-EA-treated rats displayed a dramatic decrease in both weekly seizure frequency and cumulative number of seizures over time. Additionally, CDDO-EA treatment prolonged the latency period between status epilepticus and the onset of the first seizure. Notably, CDDO-EA treatment also demonstrated an antiepileptic effect in rats with chronic epilepsy. Histological and biochemical analyses revealed a significant reduction in inflammatory cytokines and notable antioxidant effects. Our findings suggest that CDDO-EA, through the activation of the Nrf2 pathway, could be a promising anti-inflammatory and antioxidant therapeutic agent for preventing epileptogenesis and modifying the development of epilepsy.

**Disclosures:** Y. Sheeni: None.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.01/C7

**Topic:** B.09. Glial Mechanisms

**Title:** Understanding microglial-cell interactions during fetal brain development

**Authors:** J. LEE<sup>1</sup>, H. KIM<sup>2</sup>, \*Y. YOO<sup>1</sup>;

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**Abstract:** Central nervous system (CNS) development represents a meticulously orchestrated process, fundamentally reliant on complex, time- and space-dependent interactions among diverse cell types. Throughout this entire developmental trajectory, the essential crosstalk occurring between various cell types establishes a critical mechanism that profoundly influences cellular state, identity, migration, pathfinding, and ultimate connectivity. Within this intricate system, the dynamic interactions and crosstalk between neuronal and glial cells are critical for

brain development. While neurons and astrocytes share a common neuroepithelial origin, microglia originate distinctly from erythromyeloid progenitors in the extraembryonic yolk sac and colonize the human forebrain as early as the 3<sup>rd</sup> post-conceptional week (PCW). This early arrival of microglia to the brain precedes the onset of pivotal processes in human cortical development, including neurogenesis, neuronal migration, and astrogliogenesis. Intriguingly, it is known that the density of microglial cells fluctuates in two distinct waves of proliferation, correlating with two different phases of radial glia (RG) cell fate commitment. The first peak in microglial density is observed at 10-12 PCW, subsequently preceding the onset of substantial neurogenesis. A second peak in density is observed at 20 PCW prior to the initiation of astrogliogenesis. Given that these distinct peaks in microglia density specifically precede key RG cell fate commitment, we hypothesized that synergistic effects stemming from specific extrinsic microglial signals profoundly impact both neuro- and astrogliogenesis, primarily through their interactions with RGs. Here, we leveraged existing single-cell RNA-seq datasets to computationally predict combinations of ligand-receptor pairs likely to influence the initiation of RG cell commitment. To identify potential candidates for ligand-receptor pairs affecting RG cell fate determination from microglia, we applied data from a series of existing single-cell transcriptomic datasets of the developing human fetal brain into an *in silico* approach. Our study not only characterized ligand-receptor pairs that potentially drive neuron and astrocyte development but also established a robust analytical pipeline. This pipeline applies existing large-scale datasets towards the systematic discovery of ligand-receptor pairs and intercellular signaling pathways that act synergistically to affect microglia-centered cell fate determination during fetal brain development.

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## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.02/C8

**Topic:** B.09. Glial Mechanisms

**Support:** JSPS KAKENHI JP20H05902  
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AMED-ASPIRE 23jf0126004h00  
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**Title:** Spatiotemporal dynamics of ATP/adenosine signaling in neuron-glia interaction

**Authors:** \*E. SHIGETOMI<sup>1,2</sup>, K. SAKAI<sup>1,2</sup>, H. SUZUKI<sup>1,2</sup>, H. YASUDA<sup>1,2</sup>, Y. FUJIMOTO<sup>1,2</sup>, S. KOIZUMI<sup>1,2</sup>;

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**Abstract:** Extracellular ATP and adenosine are key purinergic mediators involved in neuron-glia communication, regulating neuronal excitation. The imbalance of extracellular ATP and adenosine is implicated in seizure and epilepsy. However, their sources and dynamics in response to neuronal activity remain incompletely understood. Here, we investigated the spatiotemporal regulation of ATP and adenosine using genetically encoded fluorescent sensors, GRAB<sub>ATP</sub> and GRAB<sub>Ado</sub>, in acute hippocampal slices of mice. Upon electrical stimulation of the Schaffer collateral, we observed a robust increase in extracellular ATP and adenosine in the striatum radiatum in the CA1 region. Pharmacological blockade of glutamatergic transmission with CNQX and D-AP5 reduced adenosine, but not ATP elevation, indicating that adenosine elevation is downstream of synaptic transmission, while ATP release depends on presynaptic activity. Chemogenetic activation of Gq-coupled GPCR signaling in astrocytes elicited localized ATP release with distinct kinetics and spatial profiles compared to synaptically driven responses. Microglial depletion by a CSF-1 receptor antagonist attenuated the adenosine response and enhanced ATP levels, suggesting that microglia are a major source or modulator of adenosine but not ATP. Inhibition of CD39, an ectoenzyme that degrades ATP, had no significant impact on either ATP or adenosine transients, suggesting that adenosine is not solely derived from extracellular ATP degradation via CD39 under our experimental conditions. Further supporting microglial involvement in the adenosine elevation, CX3CL1-induced activation of microglia enhanced adenosine elevation. These findings collectively indicate that ATP and adenosine are regulated by partially independent pathways during neuronal excitation. While ATP is predominantly of neuronal or astrocytic origin, adenosine appears to involve microglial activity, challenging the classical model of adenosine as a mere degradation product of extracellular ATP. Our results highlight the complex, cell-type-specific regulation of purinergic signaling and underscore the need to consider the distinct contributions of neurons, astrocytes, and microglia in interpreting extracellular purine dynamics.

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## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR206.03/C9

**Topic:** B.09. Glial Mechanisms

**Support:** AMED JP24zf0127010  
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program for Bridging the gap between R&d and the Ideal society (society 5.0) and Generating Economic and social value (BRIDGE)

**Title:** Visualization of microglial phenotypic changes using P2Y12 receptor-targeted compound in two-photon imaging and MRI

**Authors:** \*Y. SAITO<sup>1</sup>, K. YATSUZUKA<sup>2</sup>, T. TSUJI<sup>1</sup>, A. SUMIYOSHI<sup>3</sup>, K. TSUJIMURA<sup>2</sup>, T. AYAKA<sup>4</sup>, H. NONAKA<sup>6</sup>, K. SATO<sup>1</sup>, H. NAKAGAWA<sup>1</sup>, K. MIKAMI<sup>1</sup>, R. Y. HARTANTYO<sup>1</sup>, H. TAKUWA<sup>4</sup>, H. YUKAWA<sup>7,5</sup>, M. HIGUCHI<sup>8,9</sup>, S. KIYONAKA<sup>2</sup>, H. WAKE<sup>1,10</sup>;

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Neuromodulation Team, Quantum Life and Med. Engin. Group, <sup>5</sup>Quantum Regenerative and Biomed. Engin. Team, Quantum Life and Med. Engin. Group, Inst. for Quantum Life Science, Natl. Inst. for Quantum Sci. and Technol., Chiba Prefecture, Japan; <sup>6</sup>Dept. of Material Chem., Grad. Sch. of Engineering, Kyoto Univ., Kyoto Prefecture, Japan; <sup>7</sup>Res. Inst. for Quantum and Chem. Innovation, Inst. of Innovation for Future Society, Aichi Prefecture, Japan; <sup>8</sup>Advanced Neuroimaging Ctr., Inst. for Med. Science, Natl. Inst. for Quantum Sci. and Technol., Chiba Prefecture, Japan; <sup>9</sup>Dept. of Neuroetiology and Diagnos. Sci., Osaka Metropolitan Univ. Grad. Sch. of Med., Osaka Prefecture, Japan; <sup>10</sup>Div. of Multicellular Circuit Dynamics, Natl. Inst. for Physiological Sciences, Natl. Inst. of Natural Sci., Aichi Prefecture, Japan

**Abstract:** Microglia, the resident macrophages of the central nervous system, play critical roles in various psychiatric and neurological disorders. Recent advances in single-cell analysis and *in vivo* imaging have revealed the phenotypic diversity of microglia. While genetic modification is a widely used approach to visualize such diversity *in vivo*, its application to primates has been challenging. In this study, we present a novel method for *in vivo* multi modal visualization of microglia using chemical labeling approach, specifically targeting P2Y12 receptors (P2Y12R), a homeostatic marker of microglia. We developed a compound that combines Ticagrelor (a P2Y12R antagonist) with SeTau-647, a fluorescence dye suitable for two-photon imaging. This compound, Ticagrelor-SeTau647, demonstrated high specificity for labeling microglia in two-photon imaging. Due to the distribution of P2Y12R in microglia, Ticagrelor-SeTau647 when injected into the cerebral ventricle of *Cx3cr1*<sup>+/GFP</sup> mice enabled enhanced visualization of microglial processes. Additionally, we synthesized a compound combining Ticagrelor with gadolinium (Ticagrelor-Gd) to visualize microglia in MRI. Ticagrelor-Gd exhibited T1 contrast effect especially in hypothalamus when injected into the mouse cerebral ventricle.

Immunohistochemical analysis revealed that Ticagrelor-Gd had no apparent effect on microglial morphology in hypothalamus. Pharmacological ablation of microglia via PLX3397 significantly eliminated this contrast effect. In cuprizone-treated mice, a progressive Multiple Sclerosis model, T1 contrast effect of Ticagrelor-Gd in hypothalamus was eliminated in correlation with microglial phenotypic changes observed in immunohistochemistry. These findings highlight the potential of a P2Y12R-targeted labeling approach for *in vivo* imaging of microglia. This method enables the visualization of microglial phenotypic changes by tracking P2Y12R expression. Moreover, given its applicability to primates, including humans, this technique may open new avenues for studying the pathophysiology of psychiatric and neurological disorders.

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## Poster

### PSTR206: Microglia Biology Within Brain Circuits

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.04/C10

**Topic:** B.09. Glial Mechanisms

**Support:** AMED JP24zf012170  
AMED JP24zf012172  
program for Bridging the gap between R&d and the Ideal society (society 5.0) and Generating Economic and social value

**Title:** In vivo visualization of microglial P2Y<sub>12</sub> receptor dynamics using chemical labeling fluorescent probes

**Authors:** \***K. SATO**<sup>1</sup>, Y. SAITO<sup>1</sup>, K. TSUJIMURA<sup>2</sup>, K. YATSUZUKA<sup>2</sup>, H. NONAKA<sup>3</sup>, S. KIYONAKA<sup>2</sup>, H. WAKE<sup>1,4</sup>;

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**Abstract:** Microglia, the resident immune cells of the central nervous system (CNS), continuously survey their surrounding environment through dynamically motile processes. The P2Y<sub>12</sub> receptor (P2RY<sub>12</sub>), specifically expressed on microglia in the CNS, is involved in their motility. However, the *in vivo* distribution of P2RY<sub>12</sub> at the level of individual processes and its relationship with microglial motility remain poorly understood. In this study, we developed a chemical labeling method to visualize P2RY<sub>12</sub> *in vivo*. A fluorescent probe, Ticagrelor-SeTau647, was synthesized by conjugating the P2RY<sub>12</sub> antagonist Ticagrelor with SeTau647, a dye suitable for two-photon imaging. Upon cortical administration in mice, microglia were clearly labeled and visualized using two-photon microscopy *in vivo*. We tested the probe in *Cx3cr1*<sup>+/GFP</sup> mice, where microglia express GFP to evaluate specificity. SeTau647 labeling overlapped with GFP-positive cells in over 90% of cases, supporting its specificity for microglia. In time-lapse *in vivo* two-photon imaging, some microglial process tips showed a marked difference between the GFP-labeled and SeTau647-labeled areas. These processes were observed when it retracts with dynamic changes of SeTau647 intensity and the maximum differences were over 3 μm in length. These findings suggest subcellular heterogeneity in P2RY<sub>12</sub> distribution among microglial processes. This method facilitates precise, high-resolution *in vivo* imaging of microglia and presents advantages over conventional genetic labeling, particularly for elucidating dynamic molecular distributions during biological processes. Notably, it does not

necessitate genetic modification, making it potentially applicable to primates and thereby expanding its translational neuroscience research applications.

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## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

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**Program #/Poster #:** PSTR206.05/C11

**Topic:** B.09. Glial Mechanisms

**Support:** JPMJSP2124

**Title:** Purine salvage pathway regulates cerebrovascular formation and microglial dynamics

**Authors:** \*R. TERUYA<sup>1</sup>, F. TSURUTA<sup>2</sup>;

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**Abstract:** The cerebrovascular network plays a critical role in maintaining brain homeostasis by ensuring the adequate delivery of oxygen and nutrients, as well as the removal of metabolic waste products. While numerous mechanisms coordinate the development and maintenance of the cerebral vasculature, the regulation of angiogenesis through purine metabolism has become of interest in recent years. There are two purine metabolic pathways: the *de novo* pathway and the salvage pathway. Previous studies have reported that inhibition of the *de novo* pathway by mycophenolic acid treatment suppresses the proliferation of vascular endothelial cells and inhibits angiogenesis. In contrast, the biological relevance of the salvage pathway in angiogenesis has remained poorly understood. In this study, we report that the salvage pathway plays an important role in cerebral vascularization and microglial control during early postnatal stages. First, to investigate the importance of the purine salvage pathway, we generated hypoxanthine-guanine phosphoribosyltransferase1 (*Hprt1*) knockout (KO) mice. HPRT is an enzyme that converts hypoxanthine to inosine monophosphate and guanine to GMP and is a responsible gene for Lesch-Nyhan syndrome (LNS) characterized by hyperuricemia and neurodevelopmental impairments. We found that *Hprt1* KO mice exhibit abnormalities in the formation of the cerebrovascular network at postnatal day 14 (P14). We also found that microglial complexity characterized by branch number was reduced, suggesting that the salvage pathway regulated by HPRT is crucial for altering microglial characteristics. Since cellular morphology is controlled by small GTPase proteins, we performed imaging mass spectrometry analysis. We observed a decrease in the amount of GMP in the *Hprt1* KO mice brain, supporting our hypothesis that reduced guanosine nucleotides attenuate the activity of small GTPases. Using two-photon excitation microscopy, we next conducted *in vivo* imaging of *Cx3cr1*<sup>GFP/+</sup> *Hprt1* KO microglia. We observed that the motility of microglial processes is decreased, suggesting that

HPRT is significant for microglial morphology and function. Given that microglial dynamics are closely associated with vascular architecture, our findings highlight microglia-vessel crosstalk during brain development mediated by the purine salvage pathway. Taken together, our data suggest a potential link to the pathophysiology of LNS, offering new insights into therapeutic strategies.

**Disclosures:** R. Teruya: None. F. Tsuruta: None.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.06/C12

**Topic:** B.09. Glial Mechanisms

**Support:** NIH:R01MH104261  
NIDA:U01DA043098  
Hope for Depression Research Foundation, USA  
Pritzker Neuropsychiatric Research Consortium

**Title:** Region- and phenotype-specific microglial gene expression in the Nucleus Accumbens: Analysis of complement, phagocytic, and metabolic markers in bHR/bLR rats

**Authors:** \*V. KUMAR<sup>1</sup>, Q. WEI<sup>5</sup>, M. FOLTZ<sup>2</sup>, H. KHALIL<sup>6</sup>, C. ZIANNI<sup>1</sup>, M. H. HAGENAUER<sup>3</sup>, E. K. HEBDA-BAUER<sup>4</sup>, M. A. EMERY<sup>7</sup>, P. M. MARAS<sup>1</sup>, D. M. KROLEWSKI<sup>4</sup>, S. KOONSE<sup>1</sup>, S. J. WATSON<sup>8</sup>, H. AKIL<sup>1</sup>;  
<sup>2</sup>Mol. and Behavioral Neurosci. Inst., <sup>3</sup>Psychology / Neurosci., <sup>4</sup>Michigan Neurosci. Inst., <sup>1</sup>Univ. of Michigan, Ann Arbor, MI; <sup>5</sup>MNI, MNI, Univ. of Michigan, Ann Arbor, MI; <sup>6</sup>The Univ. of Michigan, Ann Arbor, MI; <sup>7</sup>Neurosci., Michigan Neurosci. Institute, Univ. of Michigan, Ann Arbor, MI; <sup>8</sup>MNI, Michigan Neurosci. Inst., Ann Arbor, MI

**Abstract:** Microglia are central to regulating synaptic connectivity, immune signaling, and neuroplasticity in the brain. Using a selective breeding strategy to model genetic temperament, our lab has recently found a link between expression of several microglia genes to individual differences in emotional behaviors, including reactivity to drugs of abuse. To explore how microglial gene expression contributes to these distinct temperaments, we selected six candidate genes based on our lab's prior genomic analyses in the bHR/bLR rat model, which exhibits stable differences in affective behavior and stress sensitivity. The selected genes represent three major functional domains of microglial biology: complement signaling (C1qA, C1qC, C3), phagocytic activity (Mfge8, Cd11b), and metabolic regulation (Ucp2). We conducted high-resolution quantitative fluorescence imaging to assess their spatial expression across distinct subregions of the nucleus accumbens (NAc), including the rostral/caudal axis and core/shell compartments.

Our initial analyses focused on C1qA, C1qC, and Mfge8:

- Expression of both C1qA and C1qC was elevated in rats bred with an inhibited and anxious phenotype (bLRs). For C1qA, cell density was marginally higher in bLRs, with no difference in expression index, suggesting more cells expressing the gene above threshold, but with similar average expression per cell. Both cell number and per-cell expression of C1qC was upregulated in bLRs, especially within the Rostral-Shell, indicating elevated complement activity in this subregion.

- Conversely, Mfge8-positive cell density was higher the Caudal-Core in rats displaying a disinhibited, high drug-seeking phenotype (bHRs), though overall expression per cell was comparable, implying distinct patterns of microglial or astrocytic phagocytic regulation. Quantitative analysis for the remaining genes—Ucp2, C3, and Cd11b—is underway. These results will be integrated to provide a comprehensive spatial and molecular profile of microglial gene expression in relation to behavioral phenotype.

Together, this work highlights region- and phenotype-specific differences in microglial gene activity within the NAc and offers new insight into neuroimmune mechanisms underlying emotional traits. Moving forward, our team aims to investigate how the expression and functional impact of these microglial genes evolve following the development of cocaine self-administration, particularly in relation to the differing propensity for drug acquisition observed between bHR and bLR phenotypes.

**Disclosures:** V. Kumar: None. Q. Wei: None. M. Foltz: None. H. Khalil: None. C. Zianni: None. M.H. Hagenauer: None. E.K. Hebda-Bauer: None. M.A. Emery: None. P.M. Maras: None. D.M. Krolewski: None. S. Koonse: None. S.J. Watson: None. H. Akil: None.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.07/C13

**Topic:** B.09. Glial Mechanisms

**Support:** NIH Grant R01AG062716

**Title:** Early life hormone manipulation in rats leads to lifelong alteration in microglial morphology and reactivity.

**Authors:** \*M. M. ANDERS<sup>1</sup>, L. K. DAVIS<sup>2</sup>, L. K. FONKEN<sup>3</sup>;

<sup>1</sup>Div. of Pharmacol. and Toxicology, The Col. of Pharmacy, The Univ. of Texas at Austin, Austin, TX; <sup>2</sup>Pharm & Tox, Univ. of Texas at Austin Dept. of Neurosci., Austin, TX; <sup>3</sup>Div. of Pharmacol. and Toxicology, Univ. of Texas at Austin, Austin, TX

**Abstract:** Microglia are resident immune cells that serve as the primary defense mechanism in the brain, constantly surveying the environment and maintaining homeostasis in the central nervous system. Sex differences in microglia morphology and activity are well-established, however, the underlying mechanisms leading to these sex differences are not well understood.

Hormonal regulation has been implicated in microglial activity, with developmental hormone exposure implicated as a key factor in establishing sex-specific phenotypes. Variations in microglial activity could contribute to sex-related differences in neurodevelopment and neuroinflammatory disorders. This study assessed how manipulating the early hormone environment alters reproductive physiology and microglial morphology and reactivity across the lifespan. During the first two days of life (postnatal day [P]0 and P1), F344 x Brown Norway rat pups received daily subcutaneous injections of either sesame oil (control) or hormone treatment. The female treatment group received testosterone propionate (TP), and the male treatment group received flutamide, an androgen antagonist. Microglial reactivity and morphology were then assessed at three developmental stages: adolescence (P30), adulthood (P150), and aging (P700). In adulthood, control males had increased microglial branching compared to control females in the hippocampus, in agreement with previous work. Early-life testosterone treatment in females increased microglial branching in the CA1 and dentate gyrus (DG) during adolescence, suggesting microglia adopted a more “masculinized” morphology. In males treated with flutamide, microglial branching was reduced in the DG in adulthood, resembling adult female branching patterns. These effects were reversed in aged animals: flutamide treatment increased microglial branching in males while testosterone treatment reduced branching in females. These findings suggest that the early life hormone environment, coupled with age-associated alterations in morphology, play an important role in the appearance of sex differences in microglial morphology.

**Disclosures:** **M.M. Anders:** A. Employment/Salary (full or part-time): Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, USA. **L.K. Davis:** A. Employment/Salary (full or part-time): Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, USA. Other; Interdisciplinary Neuroscience Program, University of Texas at Austin, Austin, TX 78712, USA. **L.K. Fonken:** A. Employment/Salary (full or part-time): Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, USA. Other; Interdisciplinary Neuroscience Program, University of Texas at Austin, Austin, TX 78712, USA.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.08/C14

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Analysis of the role of the hematopoietic prostaglandin D<sub>2</sub> synthase in microglia.

**Authors:** \***M. NITTA**, I. MOHRI, M. TANIKE, M. TACHIBANA;  
United Grad. Sch. of Child Development, Osaka Univ., Suita, Japan

**Abstract:** Prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), a pro-inflammatory mediator in brains, is produced by two synthases, hematopoietic prostaglandin D synthase (HPGDS) and lipocalin-type prostaglandin D synthase. While HPGDS has been shown to be involved in neuroinflammation in several neurological diseases and is predominantly expressed in microglia within the brain, its role in microglial functions remains unclear. To examine the role of HPGDS-PGD<sub>2</sub> pathway in microglial function, we investigated the cellular properties of microglia lacking HPGDS expression using primary cultured microglia obtained from *HPGDS*<sup>-/-</sup> mice. We isolated primary microglia from the cerebral cortex of neonatal (postnatal day 0-2) *HPGDS*<sup>-/-</sup> and wild-type (WT) C57BL/6J mice. We compared their proliferation, mobility, phagocytic activity, morphology, and RNA expression profiles. Compared to WT, primary microglia from *HPGDS*<sup>-/-</sup> mice exhibited similar proliferation (BrdU assays: mean difference of absorbance, 0.17 SD 0.05 and 0.16±0.05, respectively) and viability (MTT assays: mean absorbance, 0.09±0.05 and 0.10±0.05, respectively). However, *HPGDS*<sup>-/-</sup> microglia exhibited higher mobility (scratch assay: wound closure rate 15 hours after scratching, 57.89%±33.29 and 24.27%±20.89, respectively) and phagocytic activities (latex beads assay: percentage of phagocytosis, 53.87%±4.17 and 47.28%±2.07, respectively) than WT. In addition, *HPGDS*<sup>-/-</sup> microglia exhibited a more circular morphology (form factor analysis: circularity, 0.43±0.20 and 0.32±0.19, respectively), suggesting the activation of microglia in an amoeboid shape. Furthermore, qRNA of *HPGDS*<sup>-/-</sup> microglia showed reduced expression of IL-10 (relative expression, 0.63±0.16 and 1.26±0.73, respectively), while the expressions of TGF-β (2.79±0.51 and 1.04±0.28, respectively) and the extracellular receptor TREM2 (2.49±0.77 and 1.05±0.31, respectively) were increased. These results suggest that the suppression of PGD<sub>2</sub> production caused by HPGDS knockout may activate microglia by suppressing the anti-inflammatory pathway of IL-10 while enhancing the pro-inflammatory pathway of TGF-β. Activated microglia may increase the expression of the extracellular receptor TREM2, enhancing microglial migration and phagocytosis. Therefore, the HPGDS-PGD<sub>2</sub> pathway in microglia may affect and modulate the function of microglia itself through inflammatory responses.

**Disclosures:** M. Nitta: None. I. Mohri: None. M. Taniike: None. M. Tachibana: None.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.09/C15

**Topic:** B.09. Glial Mechanisms

**Title:** Evidence that 4 days in a complex environment alters the structure of microglia in rat visual cortex

**Authors:** \*G. S. WITHERS<sup>1,2</sup>, K. BAKER<sup>2</sup>, S. WALSH<sup>2</sup>, L. GARCIA VARGAS<sup>3</sup>, C. S. WALLACE<sup>1,2</sup>;

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**Abstract:** Housing in a complex environment (EC) is natural stimulation that has been used to identify the time course of transcriptional and cell structural changes associated with experience-dependent plasticity in intact animals. Previous work using this model found changes in dendritic length and astrocyte area in layer II/III of primary visual cortex after only 4 days in weanling age male rats compared to those housed individually (IC). Evidence suggests that microglia play a role in regulating the cellular microenvironment in association with synaptic plasticity. Thus, we tested for differences in the structure of microglia at sites expressing rapid onset neuroanatomical plasticity in this short duration EC/IC model. Free-floating vibratome sections (50µm thick) containing visual cortex (OC1, OC2) from littermate pairs were immunostained for the microglial protein Iba1, and digital images were acquired using a Leica SP5 confocal, or a Leica DME microscope. All processing and data acquisition were conducted blind to experimental condition. No differences were found in the number of microglia per image (EC, 53, SD=18 SD; IC, 47, SD=23). A subset of individual microglia contained within sections were selected and quantified using a variety of methods, including manual tracing or binarization of thresholded images with NIH ImageJ. Regardless of the method, microglia from animals housed in the EC showed a significant increase in size. One method involved simply tracing the perimeter of randomly selected cells stained with DAB ( $p < 0.05$ ; EC, 1313µm +/- 452 SD; IC, 1070µm +/- 455 SD, 9 animals from 3 litters). Higher resolution analysis traced individual cells stained with DAB, or immunofluorescence, distinguished between anterior (OC2) and posterior (OC1) sections of visual cortex, and separated Layers II/III from Layer IV. In those analyses, significant differences were found in both layers II/III and IV of OC1, and while EC > IC in OC2 numerically, the differences were not significant. Whether these changes in microglia reflect dynamic homeostatic adaptation to levels of neuronal activity, or indicate direct support of ongoing plasticity remains unclear.

**Disclosures:** G.S. Withers: None. K. Baker: None. S. Walsh: None. L. Garcia Vargas: None. C.S. Wallace: None.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.10/C16

**Topic:** B.09. Glial Mechanisms

**Support:** ItiNeurostra - Strasbourg  
Doctoral School of Strasbourg (ED414)

**Title:** Role and mechanisms of leptin transport by microglia in the median eminence

**Authors:** \*B. JOFFRE<sup>1</sup>, S. ORY<sup>2</sup>, S. GASMAN<sup>3</sup>;

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**Abstract:** Leptin is a hormone secreted by adipose tissue which acts in the median eminence (ME) of the hypothalamus to induce satiety and regulate appetite. In pathological condition such as obesity, leptin is produced in large quantities, but its action is impaired. This is known as leptin resistance and the reasons of this phenomenon are still not totally understood. One hypothesis is that leptin's access to its targets is impaired. Previous work has proposed that tanycytes, which are specialized hypothalamic ependymoglia cells, lining the floor of the third ventricle, convey leptin to the ventricle lumen by transcytosis after leptin crosses fenestrated vessels. Microglia, the resident immune cells of the central nervous system, plays a pivotal role in the development of hypothalamic inflammation in obesity. As leptin modulates microglia activity, we wondered whether microglia could alter leptin availability in the ME. To address this question, we performed *in vitro* pulse-chase experiments with primary cultures of microglia from the ME using fluorescent leptin. Confocal microscopy analysis showed that leptin is rapidly endocytosed by microglia and reaches EEA1-positive endosomes before being sorted into Rab11-positive ones. Leptin colocalizes only partially with the Rab7-positive endosomes and the lysosomal marker Lamp1. Elisa assays showed that leptin is released by microglia, indicating that leptin does not reach the degradative pathway once endocytosed, but is rather released by microglia. Whether leptin trafficking is altered in condition of neuro-inflammation will be further addressed by studying the role of saturated fatty acids on microglia, one contributor to leptin resistance.

**Disclosures:** B. Joffre: None. S. Ory: None. S. Gasman: None.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.11/C17

**Topic:** B.09. Glial Mechanisms

**Support:** K00AG068442-05

**Title:** Microglia regulate adult hippocampal neurogenesis via interleukin-6 classic- and trans-signaling

**Authors:** \*R. W. CASTRO<sup>1</sup>, S. CHOI<sup>2</sup>, R. E. TANZI<sup>3</sup>;

<sup>1</sup>Neurol., Massachusetts Gen. Hosp., Medford, MA; <sup>2</sup>Genet. and Aging Res. Unit, Massachusetts Gen. Hosp. and Harvard Med. Sch., Charlestown, MA; <sup>3</sup>Massachusetts Gen Hosp, Harvard Med. Sch., Charlestown, MA

**Abstract:** Recent advances have identified microglia and interleukin-6 (IL-6) as regulators of adult hippocampal neurogenesis (AHN). However, the mechanisms underlying this regulation remain unclear. Here, we demonstrate that IL-6 classic- and *trans*-signaling yield a nearly identical homeostatic state in microglia, while IL-6 *trans*-signaling also regulates the differentiation of rat adult hippocampal neural stem cells (RAH-NSC) *in-vitro*. We also identify



mechanisms that induce interleukin-6 receptor (IL-6R) shedding by microglia *in-vivo*. Finally, we generated conditional knockout mice that lack IL-6R expression exclusively in microglia and detected impaired neuronal maturation and cognitive deficits.

**Disclosures:** R.W. Castro: None. S. Choi: None. R.E. Tanzi: None.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.12/C18

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Xeno-free, efficient derivation of ipsc-derived microglia for neuroimmunology research

**Authors:** \*N. A. J. OLIVEIRA<sup>1</sup>, K. R. LEWKOWICZ<sup>1</sup>, P. A. CLOW<sup>3</sup>, J. A. MCDONOUGH<sup>2</sup>, W. C. SKARNES<sup>4</sup>;

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**Abstract:** Microglia are essential components of the central nervous system, playing pivotal roles in brain development, homeostasis, neurodegeneration, and aging. Due to their importance, microglia are widely used in basic research and are emerging as promising candidates for *in vivo* cell therapy. Induced pluripotent stem cell (iPSC)-derived microglia offer a scalable source of cells for both basic and preclinical studies. In this study, we employed CRISPR-Cas9 to generate inducible microglia (i-Microglia) by integrating a doxycycline-inducible cassette encoding six transcription factors (6-TF) into the CLYBL safe harbor locus (Dräger et al. 2022). This strategy enables the generation of i-Microglia in less than two weeks. To adapt the protocol for clinical use, we replaced Matrigel with the xeno-free matrix Laminin-521. The resulting microglia expressed canonical markers (IBA1, CD68, and P2RY12) as early as day 6 of differentiation. Notably, P2RY12 expression, a specific microglia marker, peaked at over 90% ( $\pm 2.75$  SD) by day 10. Functional assessment via phagocytosis assays using pH-sensitive fluorescent zymosan beads (phRodo) revealed that over 75% ( $\pm 3.32$  SD) of the cells internalized beads within 2.5 hours, as quantified by flow cytometry. We further evaluated immune activation by profiling the expression of key surface markers under basal and LPS-stimulated conditions. By day 11, i-Microglia expressed activation markers such as CD40, CD80, CD83, CD86, and HLA-DR. Upon LPS stimulation, all markers were upregulated. The most significant increases were observed for CD80 ( $P < 0.01$ ) and CD83 ( $P < 0.033$ ). In conclusion, we demonstrate that combining inducible transcription factor expression with xeno-free culture conditions enables the rapid and scalable generation of functional microglia. This platform is suitable for preclinical and potentially clinical applications, including transplantation protocols. Compared to conventional methods requiring over a month to produce mature microglia, our approach offers a faster and more cost-effective alternative. The CLYBL 6-TF-iMG KI1/KI2 iPSC line is available for academic and for-profit institutions from the JAX iPSC repository ([jax.org/ipsc](http://jax.org/ipsc)).

**Disclosures:** N.A.J. Oliveira: None. K.R. Lewkowicz: None. P.A. Clow: None. J.A. McDonough: None. W.C. Skarnes: None.

**Poster**

**PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.13/C19

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Isolation and Functional Characterization of Human Primary Microglia from Post-Mortem Brain Tissue

**Authors:** \*M. BSIBSI<sup>1</sup>, C.-C. HSIAO<sup>2</sup>, L. SCHMITZ<sup>2</sup>, N. CHUNDURI<sup>3</sup>, L. GEERTS<sup>3</sup>, M. VLAMING<sup>3</sup>;

<sup>1</sup>Charles River, Leiden, Netherlands; <sup>2</sup>Neuroimmunology Res. Group, Netherlands Inst. for Neurosci., Amsterdam, Netherlands; <sup>3</sup>Biotherapeutics Drug Discovery, Charles River Labs., Leiden, Netherlands

**Abstract:** Microglia are the brain's resident immune cells and are professional phagocytes in the central nervous system (CNS) and play an essential role in both physiologic and pathological processes of the CNS. Therefore, microglia cells are considered a potential therapeutic target for neurodegenerative diseases and are considered a potential therapeutic target for neurodegenerative diseases. Human primary microglia derived from post-mortem tissue offer a physiologically relevant model to study their role in neurodegenerative diseases. We developed a rapid 4-hour protocol combining density gradient centrifugation and CD11b-based magnetic selection to isolate viable microglia from fresh post-mortem human brain tissue from the Netherlands Brain Bank. From over 100 donors, we obtained on average 450,000 microglia per gram of white matter and 145,000 per gram of grey matter. Cerebrospinal fluid (CSF) pH positively correlates with viable cell yield, while donor age and post-mortem delay do not significantly impact cell viability. This protocol provides a reliable platform for isolating high-quality human microglia, enabling studies on microglial phenotypes and their roles in neurological and psychiatric disorders. Therefore, we developed multiple *in vitro* assays to study the activation and the function of microglia including phagocytosis assay, inflammasome and toll like receptors activation assays. Isolated microglia exhibited actin-dependent phagocytosis of human myelin and pHrodo-labeled particles, confirmed via high-content live-cell imaging. TLR4 and TLR7/8 stimulation induced concentration- and time-dependent secretion of TNF- $\alpha$  and IL-6, which was suppressed by dexamethasone. LPS priming followed by nigericin exposure triggered NLRP3 inflammasome activation with robust IL-1 $\beta$  and IL-18 release, blocked by MCC950. Taken together, we successfully optimized protocol enables reproducible isolation of functional primary human microglia from post-mortem brain tissue. The isolated cells retain key immune functions and responsiveness to pharmacological modulation, providing a physiologically relevant model for investigating microglial behavior in human neuroinflammatory and neurodegenerative conditions.

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**Poster**

**PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.14/C20

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Biological significance of using primary microglial cell culture vs. BV-2 immortalized cell line.

**Authors:** \*K. UMPORNPUN, H. J. VEKARIA, M. ZAMORANO, B. B. OLDHAM, R. ESKANDARI, B. A. MILLER;  
Neurosurg., Med. Univ. of South Carolina, Charleston, SC

**Abstract:** Microglial cells are important mediators of the inflammatory response following brain injury, as they can be activated through different receptors, triggering the release of inflammatory cytokines such as TNF- $\alpha$ . In this study, we explore the effects of various concentrations of hemoglobin (Hgb) using the BV-2 microglial cell line and primary microglial cells to compare whether BV-2 cells' inflammatory response to Hgb works in the same way as primary microglial cells. To investigate this, experiments were conducted using a BV-2 microglial cell line and a primary microglial cell culture from postnatal day 1 rats. Both BV-2 microglial cells and primary microglial cells were incubated under standard conditions (37°C) for 24 hours. The pro-inflammatory cytokine TNF- $\alpha$  was analyzed to assess the inflammatory response, mitochondrial function was assessed using the Seahorse system, immunohistochemical analysis was done to analyze Caspase-3 expression, and a lactate-dehydrogenase assay was done to determine cytotoxicity levels in both groups. The results showed that TNF- $\alpha$  release in BV-2 cells is significantly lower than in primary microglial cells by tenfold at 0.01 mg/mL concentration of Hgb. Both the pro-inflammatory and metabolic responses of BV-2 cells are blunted. BV-2 cells are reactive to Hgb, producing cytokines such as TNF- $\alpha$ . However, although both BV-2 and primary microglial cells show activated responses, their TNF- $\alpha$  expression levels were significantly higher in primary microglia along with having greater metabolic dysfunction, indicating a higher sensitivity to Hgb. This demonstrates the importance of primary microglia as a model for brain injury.

**Disclosures:** K. Umpornpun: None. H.J. Vekaria: None. M. Zamorano: None. B.B. Oldham: None. R. Eskandari: None. B.A. Miller: None.

**Poster**

**PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.15/C21

**Topic:** B.09. Glial Mechanisms

**Title:** In Vivo Functional Imaging of Brain Immune Cells Using Temperature-Sensitive Quantum Dots

**Authors:** \*S. TAKEMOTO<sup>1</sup>, M. HANDA<sup>1</sup>, S. WAKITA<sup>1</sup>, T. TORIMOTO<sup>2</sup>, H. YUKAWA<sup>1</sup>, H. TAKUWA<sup>1</sup>;

<sup>1</sup>QST, Inage-ku, Chiba-shi, Chiba, Japan; <sup>2</sup>Nagoya Univ., aichi, Japan

**Abstract:** The brain is a highly complex organ responsible for maintaining homeostasis and regulating bodily functions. Among the diverse cell populations in the brain, immune cells, such as macrophages and glial cells, play critical roles in immune surveillance as well as in the pathophysiology of disorders such as stroke and dementia. However, the functional dynamics of these cells in vivo remain poorly understood, primarily owing to the lack of tools for visualizing their functional states within the living brain. In this study, we focused on intracellular temperature as a potential biomarker of immune cell activity and employed temperature-sensitive quantum dots (QDs) as nanoscale fluorescent sensors to monitor cellular functions in vivo. Using CX3CR1-GFP mice, we implanted a cranial window and allowed a two-week recovery period. We then administered an intracerebral injection of fluorescent QDs, and after one week, we performed in vivo two-photon microscopy imaging (920 nm excitation) under wakeful conditions. To capture functional changes during inflammation, we administered lipopolysaccharide (LPS) and imaged the same field of view at hourly intervals for 3 h. Image analysis and immunostaining confirmed that the QDs were internalized by the immune cells in the brain. We then extracted both intracellular temperature and motility parameters from the fluorescence signals within individual cells. Post-LPS injection, temperature and motility showed a marked shift compared to those at the baseline, suggesting that QD-based thermosensing can reveal functional alterations in immune cells under inflammatory conditions. Our results demonstrate that QD-based thermometry is a promising approach for visualizing immune cell function in vivo. This technique could facilitate elucidation of disease mechanisms and development of targeted therapeutics by enabling direct observation of immune cell behavior in the living brain.

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**Poster**

**PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

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**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** American Association for Cancer Research-Bosarge Family Foundation-  
Waun Ki Hong Regenerative Cancer Medicine Award 19-40-60-OLIV  
NIH R01CA242158  
NIH R01AG085860  
Rutgers Cancer Institute of New Jersey (CINJ)

**Title:** Cisplatin-induced disruption in reward-motivated behavior is associated with microglial reactivity and impaired medium spiny neuron morphology in the striatum

**Authors:** \*Z. WRIGHT<sup>1</sup>, D. J. TAYLOR<sup>1</sup>, A. GONZALEZ<sup>2</sup>, S. ISHRAT<sup>1</sup>, A. OLIVEROS AMAYA<sup>1,3</sup>;

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**Abstract:** Chemotherapy revolutionized treatment for cancer, resulting in a substantial decrease in mortality. In the United States alone, there were an estimated 18.1 million cancer survivors in 2022 - a number projected to reach 26.0 million by 2040, highlighting the positive impact of chemotherapy on survival outcomes. However, prolonged exposure to genotoxic treatment can lead to chemotherapy-induced cognitive impairment (CICI). Emerging evidence shows that certain brain regions, such as the hippocampus and prefrontal cortex, are particularly vulnerable to neurotoxicity by cisplatin, a platinum-based compound used in the treatment of numerous cancers. However, the adverse effects of cisplatin on emotive function and neuronal structure in the striatum, a forebrain structure involved in cognition and reward processing, remain to be elucidated. To fill this knowledge gap, we utilized a mouse model that resembles a clinically relevant cisplatin treatment regimen, where 3-month-old C57BL/6J female mice were administered 1 or 3 cycles of treatment. Our preliminary data suggest that cisplatin disrupts nesting behavior in mice, a reward-motivated phenotype akin to activities of daily living (ADL) in humans. Our preliminary data also indicate that the A<sub>2A</sub> receptor antagonists KW6002 and caffeine attenuate cisplatin-induced nesting impairments. To determine whether cisplatin negatively affects cellular hallmarks of neuronal function associated with impaired reward-motivated behavior, we characterized dendrite spine density via Golgi-Cox staining and IMARIS 3D reconstruction of medium spiny neurons (MSNs), which revealed impairments in dendrite spine density of ventral striatum (VS) MSNs. Importantly, neuroinflammatory microglia activation is thought to be a contributing factor to cognitive impairments in CICI. Using immunofluorescent microscopy with antibodies specific to microglia (Iba-1), the pro-inflammatory marker CD68, and synaptic markers, we investigated microglial reactivity in the VS and found significant increases in Iba1<sup>+</sup> microglia density. Given that microglia maintain homeostatic cellular function by engulfment-mediated removal of synapses, we are exploring aberrant synaptic engulfment by microglia in this structure. Our findings suggest that cisplatin impairs nesting-related reward-motivated behavior, striatal MSN morphology, and that microglial activation may be associated with emotive dysfunction in CICI. In summary, our studies identify novel therapeutic targets that can be targeted to improve the quality of life for cancer survivors.

**Disclosures:** Z. Wright: None. D.J. Taylor: None. A. Gonzalez: None. S. Ishrat: None. A. Oliveros Amaya: None.

**Poster**

**PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.17/C23

**Topic:** B.09. Glial Mechanisms

**Support:** National Natural Science Foundation of China (Nos. 82174499)

**Title:** Microglia-Derived Interleukin-6 Triggers Astrocyte Apoptosis in the Hippocampus and Mediates Depression-Like Behavior

**Authors:** \*S. SHEN;  
Fudan Univ., Shanghai, China

**Abstract:** In patients with major depressive disorder (MDD) and animal models of depression, key pathological hallmarks include activation of microglia as well as atrophy and loss of astrocytes. Under certain pathological conditions, microglia can inflict damage to neurons and astrocytes. However, the precise mechanisms underlying how activated microglia induced astrocyte atrophy and loss remain enigmatic. In this study, a depression model induced by chronic social defeat stress (CSDS) is utilized. The results show that CSDS induces significant anxiety- and depression-like behaviors, along with notable astrocyte atrophy and apoptosis, microglial activation, and elevated levels of microglial interleukin-6 (IL-6). Subsequent studies demonstrate that IL-6 released from activated microglia promotes astrocyte apoptosis. Furthermore, the knockdown of the P2X7 receptor (P2X7R) in microglia, which is implicated in the stress response, reduces stress-induced microglial activation, IL-6 release, and astrocyte apoptosis. Direct inhibition of microglia by minocycline corroborates these effects. The selective knockdown of IL-6 in microglia and IL-6 receptors in astrocytes effectively mitigates depression-like behaviors and reduces astrocyte atrophy. This study identifies microglial IL-6 as a key factor that contributes to astrocyte apoptosis and depressive symptoms. Consequently, the IL-6/IL-6R pathway has emerged as a promising target for the treatment of depression.

**Disclosures:** S. Shen: A. Employment/Salary (full or part-time): Fudan University.

**Poster**

**PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.18/C24

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** R01AG078758

**Title:** Circadian rhythm disruption attenuates maternal caregiving behaviors and decreases microglia density in postpartum mice

**Authors:** \*C. R. GIBSON<sup>1</sup>, B. ROUTH<sup>2</sup>, L. K. FONKEN<sup>3</sup>;

<sup>1</sup>The Univ. of Texas at Austin, Austin, TX; <sup>2</sup>Inst. for Neurosci., Univ. Of Texas At Austin Interdisciplinary Neurosciences Program, Austin, TX; <sup>3</sup>Div. of Pharmacol. and Toxicology, Univ. of Texas at Austin, Austin, TX

**Abstract:** The maternal brain changes drastically during gestation and the postpartum period to support infant attachment and the development of caregiving behaviors. During pregnancy, the neuroimmune system undergoes dynamic changes, with peripartum decreases in microglia density returning to prepartum levels soon after parturition. Microglia are regulated by the circadian system, and significant circadian disruptions lead to neuroinflammation. In the postpartum period, maternal sleep and circadian rhythms can be severely disrupted by offspring. Aberrant neuroinflammation has been tied to depressive like and other mood related behaviors. We hypothesized that circadian rhythm disruptions would negatively impact neuroimmune recovery in postpartum mice and cause females to exhibit altered mood-related behaviors and impaired maternal care to pups. Circadian disruption was induced in postpartum female C57Bl/6 mice starting on the day of parturition with a “jet lag” model of six-hour light onset chronic phase advancements (CPA) every four days. Behavior tests assessed mood-related behaviors (sucrose preference, splash test), as well as maternal care (pup retrieval and interaction, nest building). Our results showed that parous CPA females exhibited lower rates of depressive-like behaviors than nulliparous CPA females in sucrose preference tests. Circadian rhythm disruption in parous females also attenuated some maternal behaviors. To determine if circadian rhythm disruptions impacted postpartum neuroimmune activity, microglia density and activity were assessed with immunohistochemistry to stain for microglia using Iba1. The effect of CPA on MPOA microglia density depended on parity, with nulliparous females having a higher density and parous females having a lower density of microglia in this area after CPA. Taken together, these results suggest that circadian rhythm disruption alters neuroimmune recovery and impacts maternal caregiving and mood behaviors. More research on circadian neuroimmune interactions during the postpartum period could lead to novel translational applications, including circadian-based postpartum depression treatments.

**Disclosures:** C.R. Gibson: None. B. Routh: None. L.K. Fonken: None.

## **Poster**

### **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.19/C25

**Topic:** B.09. Glial Mechanisms

**Support:**

CNCD Seed Grant  
NIMH K99/R00 Pathway to Independence Award #MH120327  
NARSAD Young Investigator Grant #31308  
Whitehall Foundation Grant #2022-08-051

**Title:** The sex-specific role of microglial glucocorticoid receptors in the effects of early-life adversity on synaptic pruning and later threat-response behavior

**Authors:** \*F. H. MROUE RUIZ<sup>1</sup>, S. CALL<sup>2</sup>, J. SHEHU<sup>3</sup>, N. OTUONYE<sup>2</sup>, J. L. BOLTON<sup>4</sup>;  
<sup>1</sup>Neurosci., <sup>2</sup>Neurosci. Inst., Georgia State Univ., Atlanta, GA; <sup>3</sup>Neurosci. Inst., Neurosci. Institute, Georgia State Univ., Atlanta, GA; <sup>4</sup>Neurosci. Inst., Georgia State Univ. Neurosci. Inst., Atlanta, GA

**Abstract:** Early-life adversity (ELA) is a robust predictor of poor mental health outcomes such as depression. Animal models are valuable tools for understanding the biological mechanisms by which this increased risk of psychiatric disorders occurs. Currently, we know that ELA alters the Hypothalamic-Pituitary-Adrenal axis, causes increased levels of corticotropin-releasing hormone (CRH), and increased threat-response behavior. We have previously reported that ELA increases excitatory input onto CRH+ neurons in the paraventricular nucleus of the hypothalamus (PVN) at postnatal day (P)10 by decreasing the amount of synaptic pruning by microglia. However, the mechanisms by which ELA impairs microglial function during brain development are unknown. Here, we aimed to determine the role of microglial glucocorticoid receptors (GR) in causing the effects of ELA on microglial function and later behavior. We employed CX3CR1-Cre<sup>+</sup>::GR-fl/+ mice to “knock down” GR expression in microglia (mGR-KD) and the limited bedding and nesting model for ELA. We assessed the effects of genotype, ELA, and sex on synapse number, microglial engulfment, and behavioral outcomes in each condition. For synapse number, we quantified the colocalization of pre- and post-synaptic markers in the PVN at P10. In a separate cohort of animals, we used the looming-shadow test to measure the response to a threat, which is dependent on excitation of PVN-CRH+ neurons. We also analyzed anxiety-like behavior in the elevated zero-maze test. Our preliminary data reveal that mGR-KD increases the number of excitatory synapses in the P10 PVN of control males, perhaps mimicking ELA, but decreases their number in ELA mice (interaction of Genotype x ELA,  $p < 0.05$ , post-hoc,  $p = 0.1$ ). The assessment of microglial synapse engulfment at P8 (prior to the emergence of the synaptic changes) is ongoing, as well as the synapse number in females. In behavioral experiments with adult mice, we found that mGR-KD results in a slower latency to react to a simulated predator threat in all mice except ELA females ( $p < 0.05$ ). In the elevated-zero maze, mGR-KD renders control males less exploratory and potentially more anxious, but does the opposite in control females. ELA does not alter time spent in the open arms in males, but it increases it in females, potentially indicating increased risk-taking behavior. Together, the data suggest that microglial glucocorticoid receptor knockdown may have differential effects, depending on the early-life experience and sex of the organism, as well as the mode of assessment and age at time of analysis. These results will have important implications in the development of therapies for at-risk children.

**Disclosures:** F.H. Mroue Ruiz: None. S. Call: None. J. Shehu: None. N. Otuonye: None. J.L. Bolton: None.

**Poster**



## **PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.20/C26

**Topic:** B.09. Glial Mechanisms

**Support:** R01MH123093-01S1  
T32GM007518  
Dr. W. Burghardt Turner Fellowship Program

**Title:** Gut microbiome-microglial interactions in a preclinical model of stress induced depression using IL-17RA deficient animals

**Authors:** \*K. C. NNAH<sup>1</sup>, Z. HAGE<sup>2</sup>, M. M. MADEIRA<sup>2</sup>, A. KOKKOSIS<sup>3</sup>, S.-A. E. TSIRKA<sup>4</sup>;  
<sup>1</sup>Stony Brook University, Neurobio. & Behavior, Stony Brook, NY; <sup>2</sup>Pharmacol. Sci., Stony Brook Univ., Stony Brook, NY; <sup>3</sup>Velocigene, Regeneron Pharmaceuticals, Tarrytown, NY;  
<sup>4</sup>Pharmacol. Sci., Univ. Med. Center, Stony Brook, Stony Brook, NY

**Abstract:** Major Depressive Disorder (MDD) affects more than 350 million people worldwide yearly. Although MDD presents in affected individuals with similar symptoms (e.g., anhedonia, physical ailments, cognitive impairment), the underlying biology is heterogeneous, involving both genetic and environmental factors. Most studies are focused on investigating MDD neuronal dysfunction, but in a subset of individuals depression presents with chronic neuroinflammation and gastrointestinal (GI) dysfunction. It has been shown that the cytokines secreted by over-reactive central nervous system (CNS) immune cells (e.g., microglia) induce changes that negatively regulate neuronal plasticity and synaptic elements. Additionally, documented changes in the gut microbiome may contribute to the establishment or exacerbation of depression through immune cells (macrophages in the periphery and microglia in the brain), as bacterial metabolites generated by gut microbiota influence the inflammatory responses elicited by them. A signaling pathway known to be implicated in chronic inflammation and proinflammatory signals involves immune cells that secrete Interleukin-17A (IL-17A), a proinflammatory cytokine known to be involved in many neuroinflammatory pathologies. However, its role in stress-induced depression is largely understudied. Microglia express IL-17RA, the receptor for IL-17A, along with peripheral gastrointestinal (GI) immune cells. IL-17A has also been shown to affect both the CNS and the GI system and thus could serve as a modulator of the neuroimmune landscape during stress-induced depression. Using a model of stress-induced behavioral changes and GI-specific IL-17RA knockout mice, the bidirectional and intricate relationship between brain function and gut homeostasis is explored.

**Disclosures:** K.C. Nnah: None. Z. Hage: None. M.M. Madeira: None. A. Kokkosis: None. S.E. Tsirka: None.

**Poster**

**PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.21/C27

**Topic:** B.09. Glial Mechanisms

**Support:** Quinnipiac University College of Arts and Sciences  
Quinnipiac Biomedical Sciences

**Title:** Sex-differences modulation of hippocampal endocannabinoid signaling by chronic oral cannabidiol in synapses and glial cells.

**Authors:** \*S. A. AZERRAD<sup>1</sup>, A. J. BETZ<sup>2</sup>, J. MATHEWS<sup>1</sup>, H. JACK<sup>3</sup>, L. CAMPOS<sup>5</sup>, P. SACK<sup>4</sup>;

<sup>1</sup>Quinnipiac Univ., Hamden, CT; <sup>2</sup>Quinnipiac Univ., Woodbridge, CT; <sup>3</sup>Col. of Arts and Sci., Quinnipiac Univ., Watertown, CT; <sup>4</sup>Quinnipiac Univ., Plainview, NY; <sup>5</sup>Quinnipiac Col., Monroe, CT

**Abstract:** The endocannabinoid system (ECS) plays a crucial role in modulating various physiological processes, including mood regulation, memory, appetite, and pain sensation. Cannabidiol (CBD) and  $\delta$ 9-tetrahydrocannabinol (THC), derived from the cannabis plant, are two widely used components for both medicinal and recreational purposes. While the psychoactive effects of THC are well studied, the therapeutic potential of CBD remains less understood. In this study, we investigated the impact of chronic oral CBD administration (20 mg/kg/day for 28 days) on hippocampal endocannabinoid signaling in male and female rats. We focused specifically on ECS-related changes at neuron and glial cells. Our findings reveal a significant downregulation of CB2 receptor expression in both sexes following CBD treatment in the hippocampal synaptosomal fraction. Our data also suggest CBD-induced alterations in microglial highlighting a possible neuroimmune component to its mechanism of action. These results suggest that the hippocampus exhibits both neuronal and glial sensitivity to chronic CBD exposure, with implications for understanding region-specific and sex-independent effects of CBD on endocannabinoid dynamics. This work contributes to a growing understanding of how CBD may modulate ECS pathways in brain regions critical to emotion and cognition.

**Disclosures:** S.A. Azerrad: None. A.J. Betz: None. J. Mathews: None. H. Jack: None. L. Campos: None. P. Sack: None.

**Poster**

**PSTR206: Microglia Biology Within Brain Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR206.22/C28

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** LSUHSC Start Up Project ID# 5497780201

**Title:** Microglia at the crossroads: serotonin, BDNF, and vascular signals in neuroplasticity and neuroinflammation

**Authors:** \*F. KLEMPIN;  
Sch. of Med., LSU Hlth. New Orleans, New Orleans, LA

**Abstract:** Growing evidence suggests that prolonged immune-inflammatory states contribute to the progression of neurodegenerative diseases and psychiatric disorders. Microglia, the brain's resident immune cells, play a central role in regulating inflammation and neuroplasticity, particularly in the hippocampus. Serotonin (5-hydroxytryptamine, 5-HT) modulates adult neurogenesis in the dentate gyrus, mediates the neurogenic effect of running, and is involved in antidepressant action. Utilizing *Tph2*<sup>-/-</sup> rats, depleted of brain serotonin, we observed age-dependent expression of 5-HT receptor subtypes (5-HTR) on sorted microglia from both knockout and control littermates, which parallels changes in brain-derived neurotrophic factor (BDNF) signaling in the hippocampus, particularly with 5-HT2b. Both 5-HT2b and BDNF expression are significantly upregulated in the absence of brain serotonin. Using additional genetically modified animal models, our data show that circulatory factors such as angiotensin-converting enzyme 2 (ACE2) and bradykinin—key regulators of cardiovascular homeostasis—also influence serotonin metabolism (ACE2) and contribute to exercise-induced neuroplasticity. Dysregulated serotonin signaling and the absence of bradykinin receptor 2 enhance microglial activation, leading to altered neuroinflammation and potentially exacerbating neurodegeneration and systemic conditions such as hypertension. We further employ spatial transcriptomics to precisely identify microglial populations and localized serotonin release in brain regions such as the dentate gyrus and hypothalamus. Together, these findings underscore the dynamic interplay between peripheral signals and microglial serotonin-mediated responses, offering promising therapeutic targets. Modulating these pathways may help reduce neuroinflammation, enhance neurogenesis, improve mood, and slow disease progression.

**Disclosures:** F. Klempin: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.01/C29

**Topic:** C.01. Brain Wellness and Aging

**Support:** CQDM Grant Faubert-SYN-347

**Title:** A multimodal assessment of the long-term effects of concussions in adults over age fifty

**Authors:** \*T. SNOWDEN<sup>1</sup>, E. SKAUG<sup>1</sup>, I. TUCCI<sup>1</sup>, S. R. SHULTZ<sup>3</sup>, J. GAWRYLUK<sup>1</sup>, J. FAUBERT<sup>4</sup>, B. R. CHRISTIE<sup>2</sup>;

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**Abstract:** Concussions are a form of mild traumatic brain injury that are being increasingly recognized as a risk factor for dementia, particularly in aging adults. However, the subtle nature of these injuries and the limitations of single-modality assessments may obscure important concussion-related outcomes. This study aimed to investigate the long-term consequences of concussions in aging adults using a multimodal approach, including neuropsychological assessment, diffusion tensor imaging and blood-based biomarker analysis. Seventy-one community-dwelling adults aged 50-81 were enrolled, and asked to complete neuropsychological testing, diffusion tensor imaging, and blood collection. Participants were grouped based on history of diagnosed or self-reported concussion, contact sport exposure, and number of past injuries. Cognitive assessments included measures of attention, memory and processing speed. Serum biomarkers included neurofilament light chain (NfL), glial fibrillary acidic protein, phosphorylated tau (pTau-217), brain derived neurotrophic factor, interleukin-10 (IL-10) and tumor necrosis factor alpha. White matter integrity was assessed using tract-based spatial statistics to evaluate fractional anisotropy (FA) and mean diffusivity (MD). Participants with a history of concussion exhibited lower serum NfL levels compared to controls (FDR-adjusted  $p < 0.05$ ). However, higher NfL levels within the concussion group were associated with poorer verbal fluency and widespread decreases in FA and increases in MD. Participants with multiple concussions showed elevated IL-10, while those with contact sport experience showed higher pTau-217 levels. ROC analysis revealed that a combined biomarker model most effectively classified concussion exposure (AUC = 0.82 for multiple concussions). This study highlights potential long-term effects following concussion that may not be detectable with traditional assessments alone. Multimodal assessment offers a more nuanced understanding of concussion sequelae in aging and may help identify those at greatest risk for cognitive decline.

**Disclosures:** T. Snowden: None. E. Skaug: None. I. Tucci: None. S.R. Shultz: None. J. Gawryluk: None. J. Faubert: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurotracker. B.R. Christie: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.02/C30

**Topic:** C.01. Brain Wellness and Aging

**Support:** RG58/23

**Title:** Neural correlates of frailty and their effects on progression to dementia and mortality

**Authors:** \*C. KAN<sup>1</sup>, J. CHEW<sup>2,3</sup>, W. LIM<sup>2,3,4</sup>, C. TAN<sup>1,4</sup>;

<sup>1</sup>Psychology, Sch. of Social Sciences, Nanyang Technological Univ., Singapore, Singapore;

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Tock Seng Hosp., Singapore, Singapore; <sup>4</sup>Lee Kong Chian Sch. of Medicine, Nanyang

Technological Univ., Singapore, Singapore

**Abstract:** Frailty is a complex clinical syndrome that increases the risk of disability, dependence, and mortality in older adults. Despite its strong prognostic value and association with cognitive aging, the neural mechanisms underlying frailty remain poorly characterized. Critically, as frailty may arise from dysfunction in multiple physiological systems, it is likely associated with multiple neurobiological changes that may negatively influence health outcomes in conjunction. This study aims to determine the cerebral correlates of frailty using neuroimaging markers of neurodegeneration, cerebrovascular disease, and structural connectivity; and examine their effects with frailty on progression to dementia, stroke incidence, and mortality. The study participants were from the UK Biobank (n = 63,509, age = 65.0 ± 7.7, female = 52.3%), who have undergone comprehensive health assessments and brain magnetic resonance imaging (MRI). We computed a frailty index (FI) using 49 self-reported health-related items based on the cumulative deficit approach. Established MRI processing pipelines were used to derive measures of cerebral volumes, cortical thickness, white matter hyperintensities (WMH), cerebral blood flow (CBF), fractional anisotropy (FA), and mean diffusivity (MD). Regression models showed that greater cerebral deficits were associated with higher FI, including lower hippocampus volume (B = -0.02, SE = 0.003, q < 0.001) and global cortical thickness (B = -0.01, SE = 0.003, q < 0.001), higher WMH volume (B = 0.04, SE = 0.003, q < 0.001) and lower cortex CBF (B = -0.03, SE = 0.009, q = 0.003), lower FA (B = -0.04, SE = 0.003, q < 0.001) and higher MD (B = 0.03, SE = 0.003, q < 0.001). Higher FI predicted progression to dementia (HR = 1.91, 95% CI = 1.56-2.34, p < 0.001), incident stroke (HR = 1.24, 95% CI = 1.07-1.42, p = 0.003), and mortality (HR = 1.48, 95% CI = 1.37-1.59, p < 0.001). Additive effects of FI and neuroimaging markers were most evident for progression to dementia and mortality. Our findings suggest that the accumulation of microstructural injury, vascular and neurodegenerative pathologies underlies frailty and co-contributes to deleterious health outcomes. Advancing our understanding of how these diverse neural processes drive frailty may improve stratification of at-risk individuals for early intervention.

**Disclosures:** C. Kan: None. J. Chew: None. W. Lim: None. C. Tan: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.03/C31

**Topic:** C.01. Brain Wellness and Aging

**Support:** Academia Sinica grant: AS-GCP-113-L02

**Title:** Transcriptomic Analysis and in Vivo Transplantation of Cultured Adult Hippocampal Neural Progenitor Cells

**Authors:** \*Y.-F. HUNG<sup>1</sup>, H.-J. CHENG<sup>2</sup>;

<sup>1</sup>Inst. of Mol. Biology, Academia Sinica, Nankang, Taiwan; <sup>2</sup>Inst. of Mol. Biol., Academia Sinica, Taipei, Taiwan

**Abstract:** In adult mammalian hippocampus, neurogenesis is prominent in the subgranular zone of dentate gyrus (DG). These adult-born neurons are functionally integrated into the existing mature hippocampal circuitry. Abnormalities in adult hippocampal neurogenesis (AHN) are implicated in human neurological disorders related to learning and memory. AHN is less efficient with aging. Our lab has been studying how aging processes change AHN in mice. We developed an efficient method to culture neurospheres from adult and aged neural progenitors in DG, and keep them as adult hippocampal neural progenitor cells (AHNPCs). Single cell RNA (sc-RNA) sequencing analysis was performed on AHNPCs to identify intrinsic factors that might regulate aging changes of these progenitor cells. We also transplanted AHNPCs into mouse DG *in vivo* to explore how these ectopic cells differentiate and integrate in the mature hippocampus. Spatial transcriptomic analysis was also used to demonstrate transplanted AHNPCs exhibit same expression profile as neighboring endogenous granule cells. Our ultimate goal is to investigate whether the cultured AHNPCs can be utilized for treating dementia-related neurological disorders.

**Disclosures:** Y. Hung: None. H. Cheng: None.

## **Poster**

**PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.04/C32

**Topic:** C.01. Brain Wellness and Aging

**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])  
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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:** Role of soluble ST2 in regulating neurodegeneration during aging

**Authors:** \*J. XU<sup>1</sup>, Y. DUAN<sup>1,2</sup>, J. ZHANG<sup>1,2</sup>, Y. QIAO<sup>1</sup>, W. ZHENG<sup>1</sup>, Y. BAO<sup>1,2</sup>, X. YANG<sup>1,2</sup>, W.-Y. FU<sup>1,2</sup>, A.-Y. FU<sup>1,2,3</sup>, N. Y. IP<sup>1,2,3</sup>;

<sup>1</sup>Div. 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; <sup>2</sup>InnoHK, Hong Kong Ctr. for Neurodegenerative Dis., Hong Kong Special Administrative Region, China; <sup>3</sup>Guangdong 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:** Aging is an important risk factor associated with neurodegeneration in various forms of dementia, including Alzheimer's disease (AD). The aging process in the brain is characterized by several interconnected processes, including neural cell senescence, chronic neuroinflammation, and increased oxidative stress, which finally leads to axonal degeneration, synaptic loss, and neuronal death. Patients with AD and mild cognitive impairment exhibit elevated plasma levels of soluble ST2 (sST2), a decoy receptor that attenuates interleukin-33 (IL-33) signaling via the ST2 receptor, suggesting its potential involvement in disease pathogenesis, particularly in neurodegeneration. In this study, we investigated the roles of sST2 in neurodegeneration. We found that sST2 levels increase in the blood circulation of mice upon aging. Following intracerebroventricular infusion of sST2, these mice showed increased serum levels of neurofilament light chain, a biomarker of neuronal damage. Moreover, these sST2-infused mice exhibited decreased neuronal cell density in the cerebral cortex, suggesting more severe neurodegeneration. Proteomic analysis of the cerebral cortex from sST2-infused mice showed increased expression of proteins associated with oxidative stress, iron metabolism and programmed cell death, suggesting that sST2 may regulate these molecular pathways in neurodegeneration. Moreover, we also showed that iron-driven oxidative stress increased in the mice with an elevated sST2 level. Thus, our findings reveal that sST2 plays a critical role in neurodegeneration, suggesting its role in aging and in AD.

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## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.05/C33

**Topic:** C.01. Brain Wellness and Aging

**Title:** Unlocking the neurochemical secrets of aging: Investigating the impact of GABA producing probiotics on healthy aging

**Authors:** \*K. SHARMA<sup>1</sup>, S. PRADHAN<sup>1</sup>, C. BLANTON<sup>1</sup>, J. OCHOA-REPARAZ<sup>3</sup>, S. NAVA<sup>2</sup>;

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**Abstract:** Aging is a gradual process of weakening bodily function that leads to decline in physical, cognitive and behavioral abilities. Gamma-amino butyric acid (GABA), a major neurotransmitter in the central nervous system, is produced by both neurons and gut bacteria, and plays a crucial role in numerous physiological functions. Notably, aging is associated with a decline in GABA production and alterations in gut microbiota. Therefore, restoring GABA production by correcting dysbiosis presents a potential strategy for managing age-related functional decline. To better understand how to support healthy aging, our study investigates the gut-brain axis and the potential of genetically modified GABA-producing probiotics, specifically P8s-GAD-Lactococcus lactis (P8) to evaluate the impact on neurotransmitter levels in fecal matter, serum, and brain tissues. These changes in neurotransmitter concentrations will be quantified using liquid chromatography-mass spectrometry (LC-MS/MS). We aim to determine whether levels of key neurochemicals, including GABA, glutamine, succinic acid, and glutamic acid, change with age, and explore if this probiotic strain, P8, can play a role in maintaining these key chemical messengers through its influence on the gut-brain axis.

**Disclosures:** K. Sharma: None. S. Pradhan: None. C. Blanton: None. J. Ochoa-Reparaz: None. S. Nava: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.06/C34

**Topic:** C.01. Brain Wellness and Aging

**Support:** NIH R01 AG053952  
R35 AG072307

**Title:** Diet Quality and Its Association with Brain Age: Baseline Results from the IGNITE Study

**Authors:** \*C. URDANETA<sup>1</sup>, L. WAN<sup>1</sup>, S. DONOFRY<sup>3,4</sup>, P. SOLIS-URRA<sup>1,5,6</sup>, M. N. KEY<sup>7,8</sup>, M. VILLARROEL<sup>1</sup>, C. MOLINA-HIDALGO<sup>2,4</sup>, H. HUANG<sup>1</sup>, G. A. GROVE<sup>4</sup>, L. OBERLIN<sup>1,9</sup>, A. MARSLAND<sup>4</sup>, M. TAYLOR<sup>10</sup>, B. SUTTON<sup>11</sup>, C. KANG<sup>12</sup>, A. KRAMER<sup>13,14,15</sup>, C. HILLMAN<sup>13,15,16</sup>, E. MCAULEY<sup>14</sup>, J. M. BURNS<sup>7</sup>, E. VIDONI<sup>17</sup>, J. M. JAKICIC<sup>18</sup>, K. I. ERICKSON<sup>4</sup>, S. JAIN<sup>1</sup>;

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**Abstract:** Objective: An estimate of an individual's brain age can be calculated based on brain structure. The difference between chronological age and brain age can be interpreted as a surrogate biomarker indicating how much “older” or “younger” a given brain is relative to the person’s chronological age. Brain age may be influenced by various genetic, environmental, and lifestyle factors including dietary habits. The Healthy Eating Index (HEI) measures dietary quality using comprehensive recommendations of Dietary Guidelines. We predicted that a higher HEI would be associated with a “younger” brain. Methods: We used baseline cross-sectional data (n=648) from the IGNITE study (Investigating Gains in Neurocognition in an Intervention Trial of Exercise). Five-hundred and six participants had complete data and were included here (mean age=69.7 ± 3.68 years, % female=63.98%). HEI was determined using the Dietary History Questionnaire II. T1-weighted structural magnetic resonance imaging scans were used to calculate brain age using BrainageR software which incorporates information regarding grey matter, white matter, and cerebrospinal fluid. Brain-PAD (Predicted Age Difference), which represents structural brain health, was calculated as the difference between brain age and chronological age. Linear regression assessed the association between HEI and brain-PAD. Chronological age, sex, education, study site, body mass index, and Image Quality Rating (IQR) of T1 scans were included as covariates. Results: In a linear regression model adjusted for the covariates higher HEI was associated with lower brain age (B = -0.76, SE = 0.29, p < 0.01) and lower brain PAD (B = -0.76, SE = 0.29, p = 0.01) indicating that individuals with a higher HEI score had a younger appearing brain than their chronological age. Conclusion: These results show an association of healthy eating with a “younger” appearing brain in late adulthood when brain atrophy and risk for dementia is greatest. Future studies examining the longitudinal effects of dietary quality improvement on brain health will aid in developing a better understanding of the mechanistic pathways.

**Disclosures:** C. Urdaneta: None. L. Wan: None. S. Donofry: None. P. Solis-Urra: None. M.N. Key: None. M. Villarreal: None. C. Molina-Hidalgo: None. H. Huang: None. G.A. Grove: None. L. Oberlin: None. A. Marsland: None. M. Taylor: None. B. Sutton: None. C. Kang: None. A. Kramer: None. C. Hillman: None. E. McAuley: None. J.M. Burns: None. E. Vidoni: None. J.M. Jakicic: None. K.I. Erickson: None. S. Jain: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.07/C35

**Topic:** C.01. Brain Wellness and Aging

**Support:** CIC-U.M.S.N.H.-2025, ICTI-2025

**Title:** Effect of a high-caloric diet on lipid profile and glucose tolerance in adult female rats .

**Authors:** \***R. MERCADO**<sup>1</sup>, M. RODRÍGUEZ GAONA<sup>3</sup>, A. SANCHEZ MOLINA<sup>3</sup>, M. FLORES-MÁRQUEZ<sup>2</sup>;

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<sup>3</sup>Univ. Michoacana de San Nicolás de Hidalgo, Morelia, Mexico

**Abstract:** Diabetes mellitus is a disease related to a high-calorie intake and associated with metabolic syndrome. In previous results we show an increase in body weight, lipid profile changes, the insulin resistance curves and the tolerance curves were different to the control group at the 240 min time. Also we measured sodium pump activity that previously was showed that serotonin increases its activity in the cerebral cortex, so, the aim of the present work was to modify the diet by increasing the glucose and fatty acids contains in the food of the rats and to explore if in adult female rats there was changes as the observed ion the male rats study. Results shows an increase of the boy weight in the group with glucose and fatty acids supplementation, also the insulin resistance curves and the glucose tolerance curves ere modify in the same group. Acknowledgements: Partially supported by: CIC-U.M.S.N.H., ICTI-MICHOACAN.

**Disclosures:** **R. Mercado:** None. **M. Rodríguez Gaona:** None. **A. Sanchez molina:** None. **M. Flores-Márquez:** None.

## **Poster**

**PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.08/C36

**Topic:** C.01. Brain Wellness and Aging

**Support:** National Research Foundation of Korea (NRF) (No.2020R1A2C2013216 and RS-2023-00265524)  
Institute of Information & Communication Technology Planning & Evaluation (IITP) grant (No. RS-2022-00155966) by the Korea government (MSIT)  
BK21-plus FOUR and Artificial Intelligence Convergence Innovation Human Resources Development programs of Ewha Womans University

**Title:** Sex-specific health risk factors and cognitive aging in a korean cohort study

**Authors:** \*J. LEE<sup>1,2,3,4</sup>, M. DEVI<sup>1,2,3,4</sup>, A. CHO<sup>1,3,5</sup>, S. KIM<sup>6</sup>, R. E. KIM<sup>7</sup>, C. SHIN<sup>6</sup>, H. W. LEE<sup>8,2,3,4,9</sup>,

<sup>1</sup>Ewha Womans Univ., SEOUL, Korea, Republic of; <sup>2</sup>Computat. Medicine, Ewha Womans Univ. Sch. Of Med., Seoul, Korea, Republic of; <sup>3</sup>Syst. Hlth. Sci. & Engin. Program, Ewha Womans Univ., Seoul, Korea, Republic of; <sup>4</sup>Neurology, Ewha Womans Univ. Sch. of Med. and Ewha Med. Res. Inst., Seoul, Korea, Republic of; <sup>5</sup>Nursing Science, Ewha Womans Univ. Sch. Of Nursing Science, Seoul, South Korea, Seoul, Korea, Republic of; <sup>7</sup>Psychiatry Dept., <sup>6</sup>Inst. for Human Genomic Study, Col. of Medicine, Korea Univ., Ansan-si, Korea, Republic of; <sup>8</sup>Dept. of Neurol., Ewha Womans Univ. Sch. Med., Seoul, Korea, Republic of; <sup>9</sup>Artificial Intelligence Convergence Program, Ewha Womans Univ., Seoul, Korea, Republic of

**Abstract:** Background: Brain aging trajectories differ between men and women, yet the specific neuroanatomical regions most affected and their sex-specific patterns remain incompletely understood. Moreover, the differential impact of modifiable health risk factors on brain structural changes and cognitive aging is not fully elucidated. This study investigated how health risk factors relate to brain volume, and cognitive performance across sexes in a large Korean cohort. Methods: We performed a cross-sectional analysis of 3,003 Korean adults (aged 49-80) from the Korean Genome and Epidemiology Study (KoGES). Participants underwent T1-weighted MRI, cognitive assessments, and detailed evaluations of lifestyle, sleep, and psychological factors. Two-way ANCOVA was used to examine age and sex interactions on various cognitive domains, particularly memory and executive function. Sex-stratified partial correlation analyses explored brain-cognition associations, adjusting for demographic and clinical covariates. Moderated mediation models analyzed whether health risk factors mediated the relationship between age and cognitive function, with education as a moderator. Serial mediation models were applied to investigate whether brain volume and health risk factors sequentially mediated the association between age and cognition in men and women. Results: Executive functions was the most impaired in both sexes, with women particularly vulnerable in later life. Notably, executive dysfunction correlated with different brain structures in men and women ( $P < 0.01$ ). In women, longer sleep latency and higher depression scores mediated age-related declines in trail-making and Stroop tests, respectively. In men, smoking exacerbated age-related Stroop performance abnormalities. Education moderated these effects, with lower education mitigating cognitive decline by aging, especially in women. Serial mediation models further revealed the association of sleep latency, depression, and smoking with specific brain regions, mediated between age and cognitive aging across sexes. Discussion and Conclusion: These findings indicate that modifiable health risk factors accelerate cognitive aging, through distinct neural pathways in men and women. Targeted, sex-specific lifestyle interventions - such as improving sleep, managing depression, and reducing smoking - could be critical for promoting healthy cognitive aging. Keywords: Sex, Brain aging, MRI, Cognition, Sleep, Health factors, Education.

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## Poster

### PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.09/C37

**Topic:** C.01. Brain Wellness and Aging

**Title:** Investigation of multi scale mechanisms underlying brain resilience to aging in healthy older adults

**Authors:** \***B. LEE**<sup>1,2</sup>, **L. JIANG**<sup>2</sup>, **S. RYALI**<sup>6</sup>, **Y. ZHANG**<sup>3</sup>, **W. CAI**<sup>4</sup>, **V. MENON**<sup>5</sup>;

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**Abstract:** Unprecedented population aging presents significant challenges to public health and society. To address these, it is essential to understand the complex mechanisms underlying resilience to aging to inform strategies for promoting brain health across the lifespan. In this study, we leveraged advanced artificial intelligence (AI) techniques and multi-scale data—including neuroimaging, biological, behavioral, and environmental measures—to model individual brain resilience to aging. We applied spatiotemporal deep neural networks (stDNNs) to predict chronological age from resting-state fMRI time series in two independent cohorts: the NKI (N = 262) and HCP-Aging (N = 398) datasets. Integrated gradients (IG) were used to identify functional circuit features contributing to model predictions. Our model demonstrated high accuracy in age prediction, achieving a Pearson correlation of 0.90 in the NKI dataset and 0.72 in the HCP-Aging dataset, without retraining. IG analysis identified key brain regions and networks associated with age prediction, including the hippocampus and angular gyrus (default mode network); dorsolateral prefrontal cortex and posterior parietal cortex (frontoparietal network); and primary motor cortex, thalamus, and caudate. Higher brain resilience—quantified by larger residuals between predicted and actual age—was associated with better performance in perceptual reasoning, overall cognitive function, and attention; lower impulsivity; reduced levels of quinolinic acid; and lower incidence of allergies, Type 2 diabetes, sleep disturbances, and substance use. Additionally, individual-level resilience feature maps derived from IG showed strong spatial correlation with NMDA receptor distribution. Together, these findings introduce a novel, explainable AI-based approach for quantifying brain resilience from fMRI and highlight key functional, molecular, cognitive, and environmental mechanisms underlying resilience to aging.

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**Poster**

**PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.10/C38

**Topic:** C.01. Brain Wellness and Aging

**Support:** NIH Grant R01-HL-102457  
JSPS 23K24748

**Title:** Age-related differences in glymphatic function and their associations with fitness and brain structure: a DTI-ALPS study

**Authors:** \*T. TARUMI<sup>1,2,3</sup>, R. UEDA<sup>4</sup>, D. ZHU<sup>5</sup>, R. ZHANG<sup>2,6</sup>;

<sup>1</sup>Natl. Inst. of Advanced Industrial Sci. and Technol. (AIST), Tsukuba, Japan; <sup>2</sup>Inst. for Exercise and Envrn. Med., Dallas, TX; <sup>3</sup>Grad. Sch. of Comprehensive Human Sci., Univ. of Tsukuba, Tsukuba, Japan; <sup>4</sup>Keio Univ. Hosp., Tokyo, Japan; <sup>5</sup>Albert Einstein Col. of Med., Bronx, NY; <sup>6</sup>Univ. of Texas Southwestern Med. Ctr., Dallas, TX

**Abstract:** Diffusion tensor image analysis along the perivascular space (DTI-ALPS) is an MRI marker of glymphatic function, which facilitates clearance of brain waste products such as amyloid- $\beta$  implicated in the pathogenesis of Alzheimer's disease and related dementias (ADRDs). Advancing age, the primary risk factor for ADRDs, is associated with significant changes in cardiorespiratory fitness and brain structure that may influence glymphatic function across the adult lifespan. Additionally, ADRD risk may vary by sex. However, it remains unclear how normal aging and sex affect glymphatic function, and how glymphatic function relates to cardiorespiratory fitness and brain structural integrity. This study aimed to (1) assess glymphatic function in healthy adults using the DTI-ALPS index, and (2) examine its associations with cardiorespiratory fitness and brain structural measures across the adult lifespan. DTI-ALPS was calculated from single-shell diffusion MRI data ( $b = 1000 \text{ s/mm}^2$ , 32 directions) acquired in 161 healthy adults (age range: 22-80 years; 105 women). Cardiorespiratory fitness was measured as peak oxygen consumption ( $\text{VO}_{2\text{peak}}$ ). Brain structure was assessed using total brain volume and white matter hyperintensity (WMH) volume. For Aim 1, multiple linear regression analysis showed that older age was significantly associated with lower DTI-ALPS index in the whole study sample ( $\beta = -0.520$ ,  $p < 0.001$ ), whereas sex ( $\beta = 0.280$ ) and the age  $\times$  sex interaction ( $\beta = -0.229$ ) were not ( $p > 0.05$ ). For Aim 2, associations of  $\text{VO}_{2\text{peak}}$  and brain structural measures with DTI-ALPS were not statistically significant in the whole sample after adjustment for age. However, age-stratified analyses revealed that DTI-ALPS was positively associated with  $\text{VO}_{2\text{peak}}$  in younger adults (age  $< 55$  years;  $\beta = 0.345$ ,  $p = 0.004$ ) and with total brain volume in older adults (age  $\geq 55$  years;  $\beta = 0.255$ ,  $p = 0.030$ ). Also, DTI-ALPS was negatively associated with WMH volume ( $\beta = -0.260$ ,  $p = 0.037$ ) in older adults. These findings suggest that glymphatic function declines with age and may be enhanced by improving cardiorespiratory fitness in younger and early middle-aged adults.

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**Poster**

**PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.11/C39

**Topic:** C.01. Brain Wellness and Aging

**Title:** Elucidating neuropeptide dynamics in aging-associated hematological disorders

**Authors:** \*S. VICENZI<sup>1</sup>, L. A. CREWS<sup>2</sup>;

<sup>1</sup>Univ. of California San Diego, La Jolla, CA; <sup>2</sup>Dept Pathol, UCSD, La Jolla, CA

**Abstract:** Multiple myeloma (MM) is a fatal plasma cell neoplasm characterized by the uncontrolled regeneration of malignant stem-like cells in the protective and inflammatory bone marrow microenvironment (BMM). The underlying molecular mechanisms remain poorly understood, as no single initiating oncogene exists. One intriguing candidate is the nervous system that innervates and controls the BMM. Neuropeptides have recently emerged as crucial regulators of tumor initiation and progression, and they can be released by the peripheral nervous system. Given the dense sympathetic, parasympathetic, and sensory innervation of the BMM, we hypothesized that neuropeptides released from peripheral nerves modulate the aged BMM and contribute to the onset and progression of MM. To address this hypothesis, we first screened a publicly available transcriptomic database (Keats lab) of 66 human MM cancer cell lines, which confirmed the presence of neuropeptide receptors in most of the screened cell lines. Next, analyzing publicly available datasets from human patient samples with plasma cell myeloma showed enrichment of specific neuropeptide receptors in aged diseased versus aged normal BMM. In vitro studies using human-derived myeloma and monocyte cell lines indicated that neuropeptides protect MM cells against MM standard-of-care drugs and polarize macrophages towards an M2-like phenotype specific to MM. Together, these data suggest that neuropeptides influence bone marrow aging by altering diverse immune cells in the BMM and contribute to the onset of age-related hematological malignancies, highlighting their potential as biomarkers for early detection as well as therapeutic targets in aging research.

**Disclosures:** S. Vicenzi: None. L.A. Crews: None.

## **Poster**

**PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.12/C40

**Topic:** C.01. Brain Wellness and Aging

**Support:** NIH Grant AG-063930  
James S. McDonnell Foundation

**Title:** Early life environmental exposures predict white matter lesion burden during midlife human adulthood

**Authors:** \*U. COATS<sup>1</sup>, M. A. PIPOLY<sup>2</sup>, M. Y. CHAN<sup>4</sup>, C. SULLINS<sup>2</sup>, A. MARTIN<sup>2</sup>, D. C. PARK<sup>5</sup>, G. S. WIG<sup>3</sup>;

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<sup>5</sup>Psychology, The Univ. of Texas At Dallas, Richardson, TX

**Abstract:** Individual socioeconomic status (SES) characteristics are associated with differences in functional brain networks, brain structure, and cognitive ability in older adults. Parallel work has examined the impacts of neighborhood-based measures of exposures among individuals. Specifically, neighborhood disadvantage has been associated with variability in brain structure and cognitive ability during multiple segments of the lifespan. We examined the extent to which early life exposures relate to midlife brain health in human individuals. Through the Midlife Brain & Environment Study (MBES; N = 149, Age range: 40-64, F = 49%), we created a census-based neighborhood deprivation score for each participant using their residential address histories. Neighborhood deprivation scores were calculated for each individual's childhood, early adolescence, late adolescence, young adulthood, and middle adulthood address, using historical census data. White matter lesion volume was calculated using T1w images. A linear regression model revealed that childhood neighborhood deprivation predicted midlife white matter lesion volume ( $\beta = 0.37, p < 0.01$ ), while controlling for age, sex, intracranial volume (ICV), and present education status. Greater childhood neighborhood deprivation status was associated with greater white matter lesion volume in midlife. Conversely, adolescence, young adulthood, and present-day neighborhood deprivation status did not predict midlife lesion volume. In addition, the association between early-life community-based exposures and midlife brain health was maintained irrespective of an individual's present neighborhood-based measures of exposures. Midlife data from a second dataset (The Dallas Lifespan Brain Study [DLBS]; N = 154, Age range: 40-65, F = 67%) was examined as a replication test. While neighborhood-based measures were not available for these participants, early life exposures were defined by the highest education level completed by either parent. White matter lesion volume was calculated on T1w images. A linear regression model showed a significant association between highest parental education level and midlife lesion volume ( $\beta = -0.21, p = 0.04$ ), wherein lower parental education status was associated with greater midlife lesion volume, while controlling for age, sex, ICV, and present education. These findings demonstrate that early-life factors are related to the degree of midlife white-matter lesions even while accounting for midlife exposures, providing evidence that there exist periods of early childhood development that are consequential for white-matter brain health during middle-age adulthood.

**Disclosures:** U. Coats: None. M.A. Pipoly: None. M.Y. Chan: None. C. Sullins: None. A. Martin: None. D.C. Park: None. G.S. Wig: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.13/C41

**Topic:** C.01. Brain Wellness and Aging

**Support:** NIH R01 AG063849

**Title:** Investigating the relationship between delirium severity and postoperative depression outcomes in older adults undergoing elective non-intracranial surgery

**Authors:** \*M. R. HESS<sup>1</sup>, B. M. KRAUSE<sup>2</sup>, M. I. BANKS<sup>3</sup>, R. C. LENNERTZ, III<sup>4</sup>;

<sup>1</sup>Univ. of Wisconsin-Madison, Madison, WI; <sup>2</sup>Dept. of Anesthesiol., Univ. of Wisconsin - Madison, Madison, WI; <sup>3</sup>Dept. of Anesthesiol., Univ. of Wisconsin, Madison, WI; <sup>4</sup>Dept. of Anesthesiol., Univ. of Wisconsin, Madison, Madison, WI

**Abstract:** Postoperative delirium (POD) is an acute disorder of consciousness that associates with poor health outcomes and development of Alzheimer's Disease and Related Dementias (ADRD). Depression is a risk factor for delirium, increasing POD incidence and severity, and while delirium incidence associates with postoperative depression severity, whether delirium severity predicts postoperative depression is unknown. Since both POD and depression associate with neuroinflammation, synaptic loss, HPA axis activation, and an altered sense of self, it is reasonable to propose that higher delirium severity may manifest as increased depression after delirium resolves. Here, we conducted an exploratory analysis of an ongoing prospective longitudinal cohort study, Interventions for Postoperative Delirium Biomarker-3 (IPOD-B3) registered with clinicaltrials.gov (NCT03124303), to investigate the relationship between delirium severity and perioperative depression. This study received IRB approval from University of Wisconsin-Madison (2015-0374). Participants  $\geq 65$  years old undergoing non-intracranial surgery with an anticipated hospital stay of  $\geq 2$  days were included ( $n = 234$ ), and assessments were performed at predefined study visits. Patients were excluded if they had a history of dementia, resided in a nursing home, or could not complete study assessments. We hypothesized that delirium severity, measured by the Delirium Rating Scale (DRS), associates with increased depression severity 1-3 months after hospitalization, measured by the Geriatric Depression Severity (GDS-15). Linear regression was used to evaluate the relationship between DRS and GDS scores, with baseline GDS values used as a covariate. Welch two sample t-tests were used to assess the relationship between delirium incidence and baseline GDS values. All analyses were performed in R (R Studio 2023.12.1 Build 402, base 4.3.2), and statistical significance was defined as  $p < 0.05$ . No significant association was found between DRS and GDS ratings at 1-3 months following surgery, indicating no association between delirium severity and postoperative depression. This may suggest that delirium incidence alone is insufficient to increase the risk for postoperative depression. Baseline GDS was not different between delirious and nondelirious groups ( $p = 0.41$ ), in contrast to previous reports that preoperative depression is associated with delirium incidence. Future analyses may investigate perioperative changes in overlapping biomarkers, such as Brain Derived Neurotrophic Factor (BDNF), in delirium severity and recovery.

**Disclosures:** M.R. Hess: None. B.M. Krause: None. M.I. Banks: None. R.C. Lennertz: None.

**Poster**

**PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H



**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.14/C42

**Topic:** G.03. Stress and the Brain

**Support:** P30AG019610 seed funding

**Title:** Chronic stress (past or concurrent) impairs spatial working memory and yet enhances spatial reference memory in adult female rats and not in middle-aged female rats

**Authors:** A. C. BANDIN, \*C. D. CONRAD;  
Psychology, Arizona State Univ., Tempe, AZ

**Abstract:** Depression is a chronic and disabling psychiatric condition that is twofold more common in women than men, with middle age being particularly susceptible. About one-third fail to improve with current treatments, emphasizing further research is needed. The goal of this research was to use a female rodent model of depression to assess two domains of cognitive function implicated in depression, hippocampal-dependent spatial ability and prefrontal cortex-dependent spatial working memory. Female rats from the National Institute on Aging were received at two ages (5 and 12 months), representing reproductive adulthood and middle-age. To produce a depressive model, rats were chronically stressed using an unpredictable restraint and mild-shaking (Peay et al., 2020, 2023). Due to stressor history being a risk factor for depression, rats exposed to stress were in two groups: stressor administered for five weeks and then ended (StrP for the past) or administered and concurrent with the cognitive tests (StrC). This produced two ages (Young, Middle-Age) and three treatments (CON, StrP, StrC). For assessing working memory, rats were tested on an 8-arm win-shift, radial arm water maze (RAWM) with four platforms at the end of each arm. When a rat found one platform, the platform was removed and the rats had to remember the locations of the remaining three platforms. By trial 4, working memory was at the highest load. The number of repeat arm entries were counted as a measure of working memory. For spatial reference memory, rats were tested on the win-stay Morris Water Maze (MWM) with a single platform in the same quadrant. The distance to locate the platform was measured over five days and a probe trial given with a platform to assess spatial abilities. We found age and stress effects for both tasks in opposite directions. For the RAWM, young rats exposed to StrP and StrC showed more working memory errors than CON. Middle-aged rats showed a similar pattern but failed to reach statistical significance. For the MWM, young rats exposed to StrP and StrC showed shorter distances to escape to the platform than to CON. No significant effect was found in middle-aged rats. These findings show that chronic stress (current or past) has opposite effects in young rats (not observed in middle-aged rats), with PFC-mediated functions being impaired and hippocampal-dependent functions being potentiated. These findings show that the beneficial effects of observed with chronic stress on hippocampal function dissipates with age and that females may show vulnerabilities to PFC mediated processes.

**Disclosures:** A.C. Bandin: None. C.D. Conrad: None.

**Poster**

**PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.15/C43

**Topic:** C.01. Brain Wellness and Aging

**Support:** T32 GM145408

**Title:** Bmal1 regulates spinal cord function in aging

**Authors:** \*P. V. DEL CIOPPO VASQUES<sup>1</sup>, D. BAKER<sup>2</sup>;

<sup>1</sup>Mayo Clin. Alix Sch. of Med., Rochester, MN; <sup>2</sup>Mayo Clin., Rochester, MN.

**Abstract:** With increasing age, there is a progressive decline in motor function, which may be rooted in spinal cord dysfunction or deterioration. The transcription factor BMAL1, a core component of the circadian clock, has been implicated in systemic aging, as its global deletion leads to premature aging phenotypes in multiple tissues. However, its role in spinal cord function remains unexplored. Here, we investigate how loss of BMAL1 affects spinal cord integrity and motor performance across lifespan. Using a BMAL1 knockout (KO) mouse model, we assessed changes to motor, sensory, and autonomic function, and performed histological and biochemical analyses on spinal cord. Our preliminary results showed that BMAL1 KO mice have a predominantly motor-related decline when compared to age-matched wild-type littermates, and they have an increased rate of aneuploidy at the cellular level. These results suggest a novel, circadian-related mechanism underlying age-associated spinal cord dysfunction with potential implications for age-related motor disorders.

**Disclosures:** P.V. Del Cioppo Vasques: None. D. Baker: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.16/C44

**Topic:** C.01. Brain Wellness and Aging

**Support:** NRF-2022R1A4A1018963  
NRF-2022R1A2C1003878

**Title:** Iron induces senescence in microglia during aging and represents a dysfunctional and phagocytic state in brain.

**Authors:** \*D. P. GUPTA<sup>1</sup>, G. SONG<sup>2</sup>, H. CHOW<sup>3</sup>;

<sup>1</sup>Catholic Kwandong University, South Korea, Incheon, Korea, Republic of; <sup>2</sup>Inst. for

Transnational Neuroscience, Dept. of Medial Sci., Catholic Kwandong Univ., Incheon, Korea, Republic of; <sup>3</sup>Sch. of Life Sci., The Chinese Univ. of Hong Kong, Hong Kong, Hong Kong

**Abstract:** During aging iron dysregulation leads to inflammation, oxidative stress, and neuronal damage causing cellular dyshomeostasis, contributing to the pathophysiology of Alzheimer's disease (AD). Iron homeostasis in microglia is crucial for cellular process phagocytosis to protect against invading agents. Iron ion dyshomeostasis causing pro-inflammatory signature, causing defective phagocytosis and phagolysosome maturation was analyzed in human AD microglia single-nucleus RNA-sequencing (snRNA-seq) dataset. We observed increased iron-accumulating senescent microglia in aged mice exhibiting significant amyloid plaque accumulation associated with AD pathology. Microglia exhibited age-dependent upregulation of senescence characteristics, including lysosomal and mitochondrial dysfunction, lipid droplet accumulation, and phagolysosome formation. In vitro, iron significantly induced senescence in microglia. Transcriptomic profiling of iron-treated microglia revealed downregulation of the immune response, mitochondrial function, homeostasis, and MHC-II activation genes and upregulation of the ferroptosis, disease-associated microglia, phagocytosis, and phagolysosome formation genes. Iron-treated microglia demonstrated increased mRNA levels of ferroptosis, senescence, homeostasis, and phagosome formation. Iron-treated microglia exhibited age-dependent increased and uncontrolled phagocytosis. We propose targeting iron-accumulating senescent microglia as a promising strategy for treating neurodegenerative diseases associated with brain aging.

**Disclosures:** D.P. Gupta: None. G. Song: None. H. Chow: None.

## Poster

### PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.17/C45

**Topic:** G.03. Stress and the Brain

**Support:** Sponsorship of Gedeon Richter Talentum Foundation in the framework of Gedeon Richter Excellence PhD Scholarship  
EFOP-3.6.3-VEKOP-16-2017-00009  
OTKA grant 143627  
TKP2021-EGA-25 grant

**Title:** Cognitive decline, microgliosis and mitochondrial dysfunction of  $\alpha$ -ketoglutarate dehydrogenase double heterozygous knockout mice

**Authors:** \*M. KOKAS<sup>1</sup>, T. KOMLÓDI<sup>1</sup>, A. BUDAI<sup>2</sup>, T. TEGLAS<sup>3</sup>, L. ZHOU<sup>3</sup>, L. TRETTER<sup>1</sup>;  
<sup>1</sup>Dept. of Biochem., <sup>2</sup>Dept. of Pathology, Forensic and Insurance Med., Semmelweis Univ., Budapest, Hungary; <sup>3</sup>Hungarian Univ. of Sports Sci., Budapest, Hungary

**Abstract:**  $\alpha$ -ketoglutarate dehydrogenase complex ( $\alpha$ KGDHc) catalyzes the oxidative decarboxylation of  $\alpha$ KG in the tricarboxylic acid cycle, producing NADH for oxidative phosphorylation and succinyl-CoA for substrate level phosphorylation.  $\alpha$ KGDHc is built up by three types of subunits:  $\alpha$ -ketoglutarate dehydrogenase (E1k), dihydrolipoyl succinyltransferase (E2k), and dihydrolipoyl dehydrogenase (E3), which is the common subunit of  $\alpha$ -keto acid dehydrogenases including pyruvate dehydrogenase complex. Earlier studies of our group demonstrated that E1k-E2k and E3 subcomplexes can generate a sizeable amount of reactive oxygen species (ROS) under pathological conditions, such as acidosis (E1k-E2k) and high NADH/NAD<sup>+</sup> ratio (E3). Other groups also published that dysfunction of  $\alpha$ KGDHc may play a role in neurodegenerative diseases. In the current study we used E2k and E3 double heterozygous knockout (DKO) C57Bl/6 middle aged male mice to characterize the *in vitro* and *in vivo* changes in the brain compared to wild type (WT) animals. Of note, Homozygous knockout of these respective genes results *in utero* death. The mRNA levels of mitochondrial and cytosolic enzymes were determined from liver samples. Mitochondria isolated from brain were used to measure mitochondrial ATP production, oxygen consumption, and ROS generation. *In vivo* experiments included behavioral tests like open field- and Morris water maze tests. Histological studies were carried out on cerebral cortex and on hypophysis. *In vitro* O<sub>2</sub> consumption and ATP production were decreased in knock out rodents when mitochondria were energized with  $\alpha$ KG. Nevertheless, ROS production was also reduced in substrate-specific manners. *In vivo* DKO mice showed minor cognitive decline in behavioral tests accompanied by cortical microgliosis and neuronal death in the Cornu Ammonis. Moreover, histological results exhibited increased levels of dynamin-related protein 1 and lower levels of mitofusin 2, peroxisome proliferator-activated receptor gamma coactivator 1-alpha. This study proved that DKO mice bear several malfunctions *in vitro*, but no phenotypical alterations were found under resting conditions. However, when animals were subjected to stress situation, compensatory mechanisms were insufficient. Thus, animals exhibited stress-related responses, ultimately leading to long-term microgliosis.

**Disclosures:** M. Kokas: None. T. Komlódi: None. A. Budai: None. T. Teglas: None. L. Zhou: None. L. Tretter: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.18/C46

**Topic:** C.01. Brain Wellness and Aging

**Support:** NIH Grant T32 AG020506

**Title:** Ipscs modeling of bmp-induced molecular and cellular changes in neurons of tauopathies

**Authors:** \*Y.-P. LI<sup>1</sup>, A. AFFANEH<sup>2</sup>, A. LINDEN<sup>1</sup>, J. GEIER<sup>1</sup>, J. ALLEN<sup>1</sup>, C.-Y. PENG<sup>1</sup>, J. A. KESSLER<sup>1</sup>;

<sup>1</sup>Neurol., Northwestern Univ., Chicago, IL; <sup>2</sup>Psychiatry, Washington Univ., St. Louis, MO

**Abstract:** Tauopathy, characterized by the deposition of tau protein in neurons or glial cells, is a common pathological feature found in many neurodegenerative diseases, including Alzheimer's disease (AD), frontotemporal dementia (FTD), and progressive supranuclear palsy (PSP). Aging is recognized as the greatest risk factor for these neurodegenerative diseases, suggesting that the aging process contributes to this shared pathophysiology. Previous research from our lab and others has demonstrated an age-dependent increase in bone morphogenic protein (BMP) signaling in both murine and human brains. Our studies have further shown that BMP signaling exacerbates tau phosphorylation and secretion in induced neurons (iNs) derived from AD-induced pluripotent stem cells (iPSCs) with varying *APOE* backgrounds. Furthermore, inhibiting BMP signaling with its antagonist Noggin prevents disease onset and progression *in vivo*, as demonstrated in both the P301S mouse model of tauopathy and the human APOE4 knock-in mouse model of AD. These findings indicate that increased BMP signaling may be part of age-related changes predisposing individuals to tauopathy. Therefore, I hypothesize that an age-related increase in BMP signaling contributes to the onset and progression across multiple tauopathies. To test this hypothesis, multiple iPSC-induced neurons with different tauopathy genetic risk factors will be used to analyze the characteristics of tau after modulating BMP signaling. My results thus far have shown that BMP4 treatment upregulates intracellular phospho-tau, promotes phospho-tau secretion, and increases four repeats (4R) tau in the P301S mutant iNs compared to the control. I am currently examining the potential downstream kinases involved in tau phosphorylation, the specific sites of phosphorylation, and the extent to which similar mechanisms mediate the effects of BMP signaling in different tauopathy cell lines.

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## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.19/C47

**Topic:** C.01. Brain Wellness and Aging

**Support:** NSF Grant 2233539  
Office of Undergraduate Research and Creative Activity

**Title:** The Impact of Gut Health on Brain and Muscle Decline

**Authors:** \*H. MOORE, C. PATTON, A. SALAZAR;  
Christopher Newport Univ., Newport News, VA

**Abstract:** Previous research in fruit flies has discovered a relationship between increasing age and a deterioration in gut health, with developing intestinal barrier dysfunction tightly linked to mortality. Because of this tight association between organismal health and gut function, several markers of aging have been investigated in order to determine the role of barrier integrity on aging phenotypes. This study examines whether intestinal barrier deterioration can impact protein aggregation within the brain and muscles. Protein aggregates are a specific aging phenotype associated with several diseases of aging and neurodegeneration, such as Parkinson's Disease and Alzheimer's Disease, with an increase in age associated with elevated protein aggregate levels. This research utilizes the knockdown of the protein Snakeskin (Ssk) in the midgut of *Drosophila melanogaster*, with Ssk knockdown inducing intestinal barrier permeability and numerous hallmarks of aging in young flies. Ssk is a septate junction protein, equivalent to mammalian tight junctions, important for maintaining the integrity of the connections between adjacent gut epithelial cells. Ssk mislocalizes in aging flies, perturbing these junctions and causing intestinal permeability. Knocking down its expression in the gut, using the GeneSwitch Gal4/UAS system in young flies, causes a decrease in barrier function and a severely reduced lifespan, in addition to other markers of aging such as gut microbiota dysbiosis, inflammation, stem cell overproliferation, and metabolic dysregulation. These experiments investigate whether manipulating Ssk expression in the gut can impact protein aggregate formation in tissues outside the gut in order to understand whether unhealthy or aging guts exhibiting barrier dysfunction may be associated with neurodegenerative diseases linked with protein aggregation in the brain and muscle. Behaviors associated with these aging phenotypes are also analyzed. Ideally, these insights will fuel a focus on intestinal health in the studies of several diseases with accompanying protein aggregation.

**Disclosures:** H. Moore: None. C. Patton: None. A. Salazar: None.

## **Poster**

### **PSTR207: The Aging Brain: The Neuroanatomy of Resilience and Risk**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR207.20/C48

**Topic:** C.01. Brain Wellness and Aging

**Support:** JSPS KAKENHI Grant Number JP24K08619  
Sophia University Faculty of Science and Technology Proposal-based  
Research Fund

**Title:** Effects of Humanin on exocytosis in senescent neurons

**Authors:** \*M. TANAHASHI, A. KOZUKA, T. NIIKURA;  
Sophia Univ., Tokyo, Japan

**Abstract:** Humanin (HN) is a 24-residue polypeptide and was initially identified as a neuroprotective factor against Alzheimer's disease (AD)-related insults. HN suppresses neuronal death caused by amyloid beta in vitro and ameliorates the memory deficit of AD mouse models. We have recently found that HN treatment increases the extracellular levels of neurotransmitters, including catecholamines (CA), in the hippocampal region of normal mice. Short-term treatment of HN also increased acetylcholine-induced CA secretion in PC12 cells, which is widely used for studying exocytosis. These findings suggest that HN has a direct effect on promoting exocytosis in neurons. To understand the mechanism, we focused on SNAP-25 (Synaptosomal-associated protein 25), one of the SNARE proteins, which induces membrane fusion between vesicles and cells. The phosphorylation at Ser187 of SNAP-25 promotes exocytosis. We found that short-term HN treatment increased the phosphorylation of SNAP-25 in PC12 cells. In chemically induced senescent PC12 cells, the expression level of SNAP-25 decreased, and its phosphorylation level was not changed by HN treatment. Consistently, the bath application experiment showed that short-term HN treatment did not restore the decreased CA secretion of senescent cells. These results suggest that HN may contribute to regulating exocytosis machinery, and cellular senescence causes its dysfunction. We have also found that long-term HN treatment recovers the suppression of exocytosis in senescent PC12 cells. However, HN does not affect SNAP-25 phosphorylation, suggesting that its mechanism differs from short-term HN treatment. Long-term HN treatment suppressed cellular senescence, as confirmed by senescence markers such as p16 and SA- $\beta$ -Gal in PC12 cells and primary cortical neurons. To further understand the effect of HN, we performed RNA-seq analysis of primary neurons and found that the expression levels of genes related to the regulation of neurotransmitter levels were increased.

**Disclosures:** M. Tanahashi: None. A. Kozuka: None. T. Niikura: None.

## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.01/C49

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

**Support:** P01AG14449  
RF1AG081286  
CA2018010  
Barrow Neurological Foundation  
Arizona Alzheimer's Consortium

**Title:** Cholinergic basal forebrain connectome dysfunction in Down syndrome with and without dementia

**Authors:** \*M. MORENO-RODRIGUEZ, S. E. PEREZ, M. NADEEM, E. J. MUFSON;  
Barrow Neurolog. Inst., Phoenix, AZ

**Abstract:** Individuals with Down syndrome (DS) are at a significantly increased risk of developing Alzheimer's disease (AD). Dysfunction of cholinergic basal forebrain neurons (CTBF), located within the nucleus basalis of Meynert (nbM) that rely on the binding of the high (TrkA) and low (p75<sup>NTR</sup>) affinity receptor with nerve growth factor (NGF) and its precursor molecular proNGF for their survival plays a pivotal role in the onset of dementia in DS. Here we analyzed alterations to CTBF proNGF/NGF system in individuals with DS and dementia (DSD+) and without dementia (DSD-), and age-matched controls (AMC). Immunohistochemical analysis assessed the number of p75<sup>NTR</sup> and choline acetyltransferase (ChAT), tau AT8 and TauC3 positive neurons within the nbM, while p75<sup>NTR</sup>, ChAT, proNGF, and TrkA protein levels were determined in the FC tissue from DSD+, DSD-, and AMC subjects using western blotting. A significant reduction in p75<sup>NTR</sup>-positive neurons was observed in the nbM of DSD+ compared to AMC, while no changes were observed in DSD- compared to either AMC or DSD+. The number of ChAT-positive cells were lower in DSD+ than in both DSD- and AMC groups. Although no significant differences were found in the number of AT8 or TauC3-positive neurofibrillary tangle (NFT) bearing neurons in the nbM between DSD- and DSD+, a greater number of AT8 positive neuropil threads (NT) and Thioflavin-S (THS)-positive NFT were found in the DSD+ cases. Cortical protein levels of p75<sup>NTR</sup> and proNGF increased, while ChAT levels significantly decreased in DSD+ compared to AMC cases, whereas TrkA levels were stable across the three groups. Cortical p75<sup>NTR</sup> protein levels positively correlated with proNGF, AT8-positive NT and ThS-positive NFTs, while cortical ChAT levels negatively correlated with AT8-positive NFTs. Our data reveal a greater loss of p75<sup>NTR</sup> CTBF neurons but an increase in cortical p75<sup>NTR</sup>/proNGF protein levels compared to similar TrkA levels suggesting compensatory response related to CTBF loss and the formation of more advanced NFT pathology in DSD+ cases.

**Disclosures:** M. Moreno-Rodriguez: None. S.E. Perez: None. M. Nadeem: None. E.J. Mufson: None.

## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.02/C50

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

**Support:** NIH Grant P01AG14449  
NIH Grant RF1AG081286  
BrightFocus Foundation CA2018010  
Barrow Neurological Foundation  
Arizona Alzheimer's Consortium

**Title:** Frontal cortex neuroinflammation in young adults with Down Syndrome



**Authors:** \*S. E. PEREZ<sup>1</sup>, Z. LESHER<sup>3</sup>, D. MORENO<sup>1</sup>, E. J. MUFSON<sup>2</sup>;

<sup>2</sup>Translational Neurosci., <sup>1</sup>Barrow Neurolog. Inst., Phoenix, AZ; <sup>3</sup>Barrow Neurolog. Intitute, Phoenix, AZ

**Abstract:** Down syndrome (DS) is characterized by developmental delays and intellectual disability and the presence of amyloid-beta (A $\beta$ ) plaques and phosphorylated tau (p-tau) bearing neurofibrillary tangles (NFTs) by their forties caused by the full or partial triplication of the chromosome 21 (Chr21). People with DS also display chronic neuroinflammation resulting from an extra-copy of inflammatory-related genes located in Chr21 (*S100B*, *IFRNA1*, *IFRNA2*, *RUNX1*, *BACE*, *DYRK1A*, *TIAMI*, *APP*). While inflammation has been examined in relation to Alzheimer's (AD) pathology and cognition in DS individuals forty years or older, little is known about similar response in young DS cases prior to AD pathology onset. Here we examined inflammation using antibodies against the microglial calcium binding phagocytic protein (Iba1), astrocytic intermediate filament glial fibrillary acidic protein (GFAP), chitinase 3 like 1 (Chi3L1/YKL-40) and the calcium binding protein S100 $\beta$  to label astrocytes as well as the lipid transporter protein apolipoprotein E (APOE) in frontal cortex (FC) grey (GM) and white matter (WM) in young adults (n=9; age range: 23 to 44 years) with DS compared to neurotypical controls (NTC, n=6) from 25 to 50 years of age. Plaque and NFT pathology was examined using antibodies against the amyloid precursor protein (APP/A $\beta$ ; 6E10), A $\beta$ <sub>1-42</sub>, A $\beta$ <sub>1-40</sub>, and the phospho-tau AT8, respectively. We found significantly lower numbers of Iba1 positive microglia in FC layers V-VI and WM in DS compared to NTD. Although there were no differences in GFAP positive astrocyte counts between groups, the number of Chi3L1 positive astrocytes was reduced in GM and WM, whereas S100 $\beta$  immunostained astrocytes were only reduced in WM in DS compared to NTD cases. By contrast, number of APOE positive astrocytes were higher in FC layers V-VI in DS. A $\beta$ <sub>1-42</sub> positive plaque number was increase in FC layers III, V-VI and WM in DS compared to NTD. Conversely, only a few APP/A $\beta$  and A $\beta$ <sub>1-40</sub> positive plaques were observed across cortical layers and WM in DS, and there were no differences between groups. Although only a few AT8 positive NFTs were seen in DS none were found in NTD cases. Correlational analysis showed strong positive associations between APOE glial positive cell number and A $\beta$ <sub>1-42</sub> plaques in layers III and V-VI and Iba1 microglia with Chi3L1 astrocyte numbers in WM in DS. Data suggests that trisomy 21 alters the number of FC glial cells in young adults with DS, that may contribute to a dysfunctional immune system prior to AD lesions and cognitive decline later in life.

**Disclosures:** S.E. Perez: None. Z. Leshner: None. D. Moreno: None. E.J. Mufson: None.

## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.03/C51

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

**Support:** NIH P01AG14449  
NIH P30AG10161  
BrightFocus Foundation  
Arizona Alzheimer's Consortium  
Barrow Neurological Foundation

**Title:** Frontal cortex heat shock proteins differentiate very old individuals with superior cognitive from normal cognitive performance

**Authors:** \*E. J. MUFSON<sup>1</sup>, B. HE<sup>2</sup>, M. MALEK-AHMADI<sup>4</sup>, S. E. PEREZ<sup>3</sup>;  
<sup>2</sup>Dept Neurobio., <sup>3</sup>Dept Translational Neurosci., <sup>1</sup>Barrow Neurolog. Inst., Phoenix, AZ; <sup>4</sup>Banner Alzheimer's Inst., Glendale, AZ

**Abstract:** Elderly individuals over 80 years of age who have episodic memory scores similar to middle-aged subjects (50-65 years old) based on the Delayed Recall portion of the Rey Auditory Verbal Learning Test (AVLT) are designated as Superagers. However, the cellular factors that contribute to the preservation or enhancement of memory in very old individuals remain poorly understood. Here, we subdivided non-demented individuals 80+ years of age based upon their last premortem episodic memory score before death from the Rush Religion Orders Study (RROS). Cognitive classification was derived from normative data from the National Alzheimer's Coordinating Center (NACC) Uniform Dataset (UDS) 2.0 to determine normal performance on the logical memory-delayed recall (LM-DR) task. Those non-demented individuals with an age at death of 80+ whose last LM-DR score was 14 or higher were classified as Superior Cognitive Performance (SCP) and those that had LM-DR scores ranging from 7 to 13 were classified as Normal Cognitive Performance (NCP). The RROS premortem cognitive assessment does not include the AVLT test. Since chaperone small heat shock proteins (HSPB) play a key role in preventing abnormal protein folding, a major factor associated with AD pathology, we assessed frontal cortex (FC) levels of HSPB1, 2, 3, 5, 6, 7, 8) from 17 SCP (age range: 82-96 years old) and 16 NCP (age range: 81-95 years old) RROS cases based upon their last LM-DR scores. Significantly higher protein levels of HSPB2 (Mann-Whitney test,  $p=0.003$ ), HSPB6 (Mann-Whitney test,  $p<0.0001$ ) and HSPB8 (Mann-Whitney test,  $p=0.001$ ) were found in SCP compared to NCP cases, while HSPB1, 3, 5 and 7 protein levels were comparable between groups (Mann-Whitney test,  $p>0.05$ ). Correlational analysis demonstrated significant positive associations between the values of HSPB2, 6 and 8 with global cognition (Spearman test,  $r>0.45$ ,  $p<0.01$ ) and LM-DR scores (Spearman test,  $r>0.45$ ,  $p<0.01$ ) across cognitive groups. Interestingly, only HSPB6 levels correlated with a single episodic memory score used by the RROS (Spearman test,  $r=0.59$ ,  $p=0.0003$ ). Similar associations were not observed for HSPB1, 3, 5 and 7 across groups. Findings suggest that select heat shock proteins involved in preventing abnormal protein folding, protein homeostasis and chaperone-like activity, play a key role in maintaining superior cognition in very old adults.

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**Poster**

**PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.04/C52

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

**Support:** Institute for Mental Health Research  
Institute for Social Science Research  
National Institute on Aging (NIA) of the National Institutes of Health  
(NIH) P30AG019610: Arizona Alzheimer's Disease Research Center  
REC Fellows Program and Arizona Alzheimer's Consortium  
ADHS Grant No. CTR057001

**Title:** Investigating fine motor degeneration and cognitive decline in a transgenic rodent model of Alzheimer's disease across the lifespan using a novel reaching task

**Authors:** \*A. MELICK<sup>1</sup>, K. CHRISTIANSEN<sup>2</sup>, H. A. BIMONTE-NELSON<sup>1</sup>, S. BEEMAN<sup>3</sup>, J. L. VERPEUT<sup>1</sup>;

<sup>1</sup>Psychology, Arizona State Univ., Tempe, AZ; <sup>2</sup>Arizona State Univ., Peoria, AZ; <sup>3</sup>Sch. of Biol. and Hlth. Systems Engin., Arizona State Univ., Tempe, AZ

**Abstract:** Alzheimer's disease (AD) is the most common form of dementia, characterized by amyloid- $\beta$  aggregates, tau tangles, and brain-wide inflammation and atrophy. As of 2025, AD is the most expensive disease in America, set to cost the U.S. \$1 trillion by 2050 (USC, 2023). These costs are partially derivative of diagnostic shortfalls, with detectable symptoms occurring at late stages when therapies are least efficacious. Current tools are expensive, with costs 13-24 months prior to diagnosis exceeding \$10k per person on average (Kvello-Alme et al., 2021). More recent developments highlight the usefulness of fine motor tasks such as finger dexterity and upper-extremity tasks in identifying early changes in fine motor decline, which may occur prior to cognitive deficits. These tasks are readily accessible and affordable, underscoring their potential in early diagnostics. In order to investigate the mechanisms underlying these tasks relative to disease progression, a cohort of male and female TgF344-AD (Tg) and wildtype (Wt) rats (n=24) were tested in a novel reaching task at 6, 12, and 18 months of age. This task uses 3 increasingly difficult bowls that require rodents to continually update their strategy to navigate bowl variability and pellet movement. This challenges the traditional single-pellet task's performance ceiling effect, which allows rodents to plateau in both speed and accuracy due to mastery of a stagnant, repetitive reach. Further, we introduce a scoring system that categorizes a reach as a success, drop, or failure, allowing for a more complex quantification of performance. At both 6 and 12 months of age, there was no significant difference in total number of reaches, but Wt rats had more successful reaches compared to Tg rats ( $p=0.041$  and  $p=0.016$ , respectively), indicating that both genotypes were capable of task completion but differed in performance. Machine learning softwares, keypoint-MoSeq and SLEAP, also identified variability in task strategy with principal component analysis of rodent paw conformation and trajectory showing differences in transition probability in a single reach and in syllable use between genotypes. Additionally, we assessed spatial learning and reference memory in the Morris Water Maze. There was no genotype difference in swim distance at 6 months of age ( $p=0.16$ ), but Tg rats at 12 months of age swam significantly longer distances to the platform ( $p=0.01$ ), demonstrating cognitive decline between timepoints. These findings point to fine

motor ability as a putative indicator of early disease onset, and that these changes may precede cognitive deficits in spatial and reference memory.

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## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.05/C53

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

**Support:** AG014449  
AG107617  
AG072599  
AG074004  
AG077103  
AG085572

**Title:** Bioinformatic analysis of Layer III and Layer V laminar regions and pyramidal neurons via digital spatial profiling (DSP) using postmortem human formalin fixed paraffin embedded (FFPE) tissue.

**Authors:** \*A. STANISAVLJEVIC<sup>1</sup>, K. W. IBRAHIM<sup>2</sup>, S. LEE<sup>2,3</sup>, M. J. ALLDRED<sup>2,3</sup>, P. STAVRIDES<sup>2</sup>, C. BARE<sup>7</sup>, R. A. NIXON<sup>2,3,4,5</sup>, S. D. GINSBERG<sup>2,3,6,5</sup>;  
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**Abstract:** Digital spatial profiling (DSP) is a recently developed technology used to perform RNA sequencing (RNA-seq) and bioinformatic analysis linked to precise spatial information from identified regions and cell types. We demonstrated that RNA profiling data can be retrieved using a modified protocol for GeoMx DSP for laminar regions of admixed cell types and groups of ~14-21 pyramidal neurons of layer III (L3) and layer V (L5) in human postmortem prefrontal cortex Brodmann area 9 (BA9) tissue from subjects with no cognitive impairment. Preliminary RNA-seq data produced by a robust and reproducible GeoMx manual slide preparation of formalin fixed paraffin embedded (FFPE) BA9 tissue was validated with several types of RNA-seq data of varying stringencies. Specifically, data processing and mining using 2 different stringency levels for probe filtering is enabled. Analysis of differentially expressed genes (DEGs) in parallel with gene set enrichment analysis (GSEA) of DEGs in L3 regions of interest (ROI) compared to L5 ROIs is being undertaken. We aim to establish potential differences in function of pyramidal neurons within discrete laminae through characterization of DEGs and biological pathway inquiry. We also present a preliminary cellular deconvolution approach

utilizing multiple established methods to understand the cellular composition of regional BA9 dissections. Probes collected and processed from human postmortem BA9 cortical tissue can be used to identify genetic expression differences in L3 and L5 admixed cell populations as well as pyramidal neurons. The present study in nondemented control subjects enables rigorous and reproducible future analyses of pyramidal neurons and their role in neurodegenerative disorders including across the Alzheimer's disease spectrum.

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## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.06/C54

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

**Support:** P01 AG014449  
P30 AG066468

**Title:** Cognitive resilience in Alzheimer's disease despite cholinergic loss in precuneus cortex

**Authors:** \*E. E. ABRAHAMSON<sup>1,2</sup>, R. MARSDEN<sup>3</sup>, V. N. PIVTORAIKO<sup>4</sup>, W. R. PALJUG<sup>5</sup>, N. ALRAQMANY<sup>6</sup>, E. J. MUFSON<sup>7</sup>, M. D. IKONOMOVIC<sup>6,2,5</sup>;

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**Abstract:** Deficits in cortical cholinergic innervation are believed to underlie cognitive impairment in Alzheimer's disease (AD). In agreement with this idea, acetylcholinesterase inhibitors are one of the few drugs with clinical benefits in AD patients. While loss of cortical cholinergic enzyme activity has been established in cases with frank AD dementia, alterations in cortical cholinergic markers during preclinical and early clinical stages, and their relationship with regional variations in amyloid- $\beta$  (A $\beta$ ) and phosphorylated tau (p-tau) concentrations, is not well understood. We measured choline acetyltransferase (ChAT) activity in Default Mode Network (DMN) hubs including frontal cortex (FC), precuneus (PreC), and posterior cingulate cortex (PCC) harvested postmortem from cases in the Rush Religious Order Study with last clinical diagnosis of no cognitive impairment (NCI) or mild AD (mAD), compared to severe AD (sAD) patients from UPitt ADRC. The NCI group was divided based on neuropathology findings into low-pathology (LP-NCI) and high-pathology (HP-NCI), representative of resistance and cognitive resilience to AD pathology, respectively. The same frozen tissue homogenates analyzed for ChAT activity were used to assay concentrations of fibrillar A $\beta$ 1-42 and soluble and fibrillar pThr181 tau. Compared to LP-NCI (resistant) cases, ChAT activity was significantly

reduced in PreC cortex from HP-NCI (resilient) cases and further stepwise reductions were observed in mAD and sAD cases. In contrast, ChAT activity was stable across LP-NCI, HP-NCI, and mAD groups in FC and PCC, showing significant reductions in these regions only in sAD. Across all clinical groups, lower ChAT activity correlated with greater A $\beta$ 1-42 concentration in PreC ( $r=-0.658$ ,  $p<0.0001$ ), weakly in PCC, and not at all in FC. Correlations between lower ChAT activity and higher pThr181 tau were significant in all three regions but were driven exclusively by high pThr181 concentration in sAD cases. Higher ratios of soluble/fibrillar pThr181 tau correlated with higher ChAT activity levels in the FC exclusively ( $r=0.5832$ ,  $P=0.0003$ ). Our results suggest that PreC cortex is selectively vulnerable to cholinergic loss, paralleling fibrillar A $\beta$  but not p-tau accumulation early in preclinical AD, in people with cognitive resilience despite high cortical concentrations of A $\beta$  and p-tau. Higher conversion of soluble to fibrillar p-tau was associated with lower ChAT activity selectively in the frontal cortex, suggesting that cholinergic projections to this DMN hub are more vulnerable to the progression of tau pathology.

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## Poster

### PSTR208: Alzheimer's Disease: Omics Approaches II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.07/C55

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

**Support:** NIH/NIA 5R01AG059627  
NIH/NIA U19AG068054  
NIH/NIA P50AG16573  
NIH/NIA P30AG066519  
Brightfocus BFF17\_0008

**Title:** Region-specific alterations in gene expression of Chromosome 21 genes in the brains of people with Down syndrome and Alzheimer's disease

**Authors:** \*S. TALLINO<sup>1,2</sup>, I. S. PIRAS<sup>3,4</sup>, M. HUENTELMAN<sup>3,4</sup>, S. BERES<sup>3</sup>, S. SCOTT<sup>5</sup>, S. WRIGHT<sup>6</sup>, E. HEAD<sup>6</sup>, R. VELAZQUEZ, Jr.<sup>1,2,4</sup>;

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**Abstract:** Down syndrome (DS) is the leading cause of early-onset Alzheimer's disease (AD) and occurs in 1/700 births in the United States. By age 40, the hallmark AD pathologies, including A $\beta$  plaques and tau tangles, are ubiquitous; similarly, regions of the brain such as the basal forebrain (BF) show volume loss via imaging and cholinergic cell loss in post-mortem

tissue. While the increase in gene dosage due to Chromosome 21 (Chr21) triplication causes DS, there is still much to learn regarding differentially expressed genes (DEGs) on Chr21 between people with AD and those with DS and AD (DS-AD), which brain regions show differential expression, and the relationship between expression of Chr21 genes and gene expression across the rest of the genome. Here, we used bulk RNAseq to assess expression in post-mortem brain samples from 25 donors with AD (age:  $86.7 \pm 8.7$ , M/F ratio: 1:1), 22 with DS-AD (age:  $74.7 \pm 16.7$ ; M/F ratio: 1.2), and 23 controls (CTL; age:  $88.1 \pm 3.8$ ; M/F ratio: 0.8) across three brain regions: the BF, middle temporal visual area (MT) and middle frontal area (MF). Data were pre-processed using Nextflow-RNAseq pipeline, and differential expression was conducted with DESeq2, followed by correction for multiple comparisons. In the BF, significant (adj-p < 0.05) Chr21 DEGs between DS-AD vs CTL included GRIK1, CFAP298, and TIAM1, while DEGs between DS-AD and AD included TIAM1, LINC01547, and SNX18P12. In the MT, significant (adj-p < 0.05) DEGs between DS-AD vs CTL included CSTB, IFNGR2, and ATP5PF, while DEGs between DS-AD vs AD included URB1-AS1, CSTB, and TMEM50B. No DEGs were significant following multiple comparison correction in the MF. Interestingly, many of the DEGs in this analysis span biological domains that are affected in AD, including regulation of synaptic plasticity (CSTB, TIAM1, GRIK1), vesicle trafficking within the endomembrane system (TIAM1, TMEM50B), transcriptional regulation (SNX18P12, LINC01547, URB1-AS1), mitochondrial energy production (ATP5PF), and neuroinflammation (GRIK1, IFNGR2). In conclusion, this work demonstrates differential DEGs in DS-AD that vary across 2 of the 3 brain regions analyzed in comparison with AD and may shed light on the molecular underpinnings of DS-AD. Future work should interrogate how overexpression of these Chr21 genes promotes pathogenesis and widespread dysregulation in DS-AD.

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## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.08/C56

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

**Support:** AG014449  
AG072599  
AG074004  
AG077103  
AG085572

**Title:** Two Hippocampal Neuron Populations Exhibit Unique Molecular Phenotypes in Aged Human Down Syndrome Brain

**Authors:** \*M. J. ALLDRED<sup>1,2</sup>, K. IBRAHIM<sup>1</sup>, H. PIDIKITI<sup>1</sup>, S. LEE<sup>1,2</sup>, E. J. MUFSON<sup>3,4</sup>, G. E. STUTZMANN<sup>5</sup>, G. CHIOSIS<sup>6,7</sup>, S. D. GINSBERG<sup>1,2</sup>;

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<sup>4</sup>Barrow Neurolog. Fndn., Phoenix, AZ; <sup>5</sup>Neurosci., Rosalind Franklin Univ. /Chicago Med. Sch., North Chicago, IL; <sup>6</sup>Chem. Biol. and Med., Sloan Kettering Inst., NEW YORK, NY;

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**Abstract:** Individuals with Down Syndrome (DS), caused by the triplication of human chromosome 21 (HSA21) present with multiple phenotypic alterations, notably behavioral and cognitive impairments along with lifelong intellectual disability. Deficits in learning, language and memory acquisition and consolidation are well established. The healthspan and lifespan of individuals with DS has greatly increased, living into their 5<sup>th</sup>-6<sup>th</sup> decades of life. This has resulted in increased diseases of aging, most notably cognitive decline associated with Alzheimer's disease (AD) dementia. Pathological AD hallmarks manifest during early mid-life in DS (noted as DS+AD), with amyloid plaques, neurofibrillary tangle formation, basal forebrain cholinergic degeneration along with cortical thinning and brain atrophy. Hippocampal dependent learning and memory circuits are impaired in DS+AD, and similar to sporadic AD, underlying cellular mechanism(s) driving preclinical disease onset are not well understood. We postulate examining single populations of key hippocampal neurons vulnerable to degeneration will elucidate cellular mechanisms and potentially help develop therapeutic targets for early intervention. Here, human hippocampal CA1 pyramidal neuron and dentate gyrus granule cell (DGC) gene expression was interrogated via laser capture microdissection combined with single population RNA-sequencing from aged individuals with DS with confirmed AD pathology compared to age- and sex-matched controls. Bioinformatic inquiry is ongoing with results postulated to identify unique differentially expressed genes (DEGs) and relevant biological pathways in each hippocampal neuron population in the DS+AD cohort compared to controls. Unique DEG analysis is postulated to identify novel targets of dysregulation in this aged disease phenotype that may be pursued for therapeutic intervention in the context of DS which also informs AD. Interrogating DEGs and downstream pathways in both CA1 pyramidal and DGCs in postmortem DS brain is likely to reveal an overall dysregulation mosaic that is neurodegenerative in nature, with both overlapping and unique patterns of dysregulation, reflecting intrinsic similarities, as well as differences, in these excitatory hippocampal neurons.

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## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.09/C57

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



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RF1AG081286 (EJM, SEP)  
P30AG10161 (Rush ADC)  
Arizona Alzheimer's Consortium (EJM)  
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Institute for Mental Health Research  
Institute for Social Science Research

**Title:** Cerebellar Perineuronal Net Dysfunction in Alzheimer's Disease

**Authors:** \*A. HASHIM<sup>1</sup>, A. YOSHIHIRO<sup>2</sup>, E. J. MUFSON<sup>2</sup>, S. E. PEREZ<sup>2</sup>, J. L. VERPEUT<sup>1</sup>;  
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Neurolog. Inst., Phoenix, AZ

**Abstract:** Keywords: Alzheimer's Disease, perineuronal nets, cerebellum  
Alzheimer's Disease (AD) is the most common type of dementia characterized by amyloid-beta (A $\beta$ ) plaque accumulation, tau bearing neurofibrillary tangles (NFTs), synaptic loss and neuroinflammation in the cerebral cortex related to cognitive decline. Several studies suggest that a loss of extracellular perineuronal nets (PNNs) contribute to neocortical AD lesions. PNNs, composed primarily of chondroitin sulfate proteoglycans (e.g., aggrecan and brevican), are critical for maintaining synaptic stability and regulating plasticity in mature neurons. PNN degradation has been associated with increased neuronal vulnerability and impaired cognitive function in both aging and AD. Chronic neuroinflammatory signaling may accelerate PNN breakdown, initiating a self-reinforcing cycle of synaptic destabilization and neuronal vulnerability. Although the cerebellum, which plays a role in motor and cognitive functions, displays amyloid plaques and neuroinflammation in AD, whether PNNs are altered in the cerebellum in prodromal AD remains a major knowledge gap. In the following study, post-mortem cerebellar cortex from individuals with a premortem clinical diagnosis of non-cognitively impaired (NCI, n=12), mild cognitive impairment (MCI, n=9), and AD (n=11) were obtained from the Rush Religious Orders Study cohort. Sections were immunostained for aggrecan, a subcomponent of PNNs. Aggrecan reactivity appeared as small granules surrounding neurons located both on the border of the molecular/granule cell layer and white matter of the cerebellar cortex. We found a significant reduction of PNN-related aggrecan immunoreactivity in the cerebellar cortex of MCI (p=0.036) and AD (p=0.0003), compared to NCI, but not between NCI and MCI. Correlational analysis revealed significant associations between aggrecan counts, episodic memory (r=0.61, p<0.001) and global cognitive scores (r=0.60, p<0.001) across clinical groups, suggesting a role for cerebellar matrix aggrecan in prodromal and frank AD. Analysis of cerebellar GFAP Iba1, and myelin basic protein in relation to PNNs in these clinical groups is ongoing. The present findings revealed a loss of PNNs in the cerebellum during the onset of AD suggesting a therapeutic target for AD.

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**Poster**

**PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.10/C58

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

**Support:** 25-00-412397-802101

**Title:** Investigating the interplay between calcium dysregulation and insulin signaling dysfunction in Alzheimer's disease using ROSMAP iPSCs-derived human neurons

**Authors:** \*S. GUPTA<sup>1</sup>, G. E. STUTZMANN<sup>2</sup>, W. GALLEGOS<sup>3</sup>, J. WHALLEY<sup>4</sup>;  
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**Abstract:** Insulin signaling regulates key CNS functions such as synaptic plasticity, memory, neuroprotection, and energy homeostasis. In Alzheimer's disease (AD), central insulin resistance is a hallmark, with 24-58% reduced insulin receptor (IR) activation and up to 90% lower IRS-1 activation. Dysregulated Ca<sup>2+</sup> signaling is a major AD pathology, impairing neuronal growth, exocytosis, and cognition. Excessive Ca<sup>2+</sup> release from the ER plays a central role in AD progression. Recent findings show that when glutamate causes an increase in intracellular calcium ([Ca<sup>2+</sup>]<sub>i</sub>), it blocks IR activation. At the same time, insulin activation of the IR reduces glutamate-induced calcium rise, implicating a two-way negative feedback loop between these two crucial pathways. This study investigates the interplay between calcium dysregulation and insulin signaling dysfunction in AD using human induced pluripotent stem cell (iPSC)-derived neurons from the Religious Orders Study and Memory and Aging Project (ROSMAP) cohort. Integrative analysis of multi-omic data from the dorsolateral prefrontal cortex (DLPFC) in ROSMAP, spanning neurons and glia, revealed a metabolic shift marked by changes in abundance of mTOR-pathway proteins, including insulin signaling mediator AKT3 and its negative regulator PTEN, as well as altered methylation of another insulin signaling mediator, AKT1. This was accompanied by increased inflammatory gene expression in microglia, as detected by single-nucleus RNA-seq. Calcium imaging demonstrated that AD neurons exhibit significantly increased ER-calcium release, which was normalized by Ryanodex, a negative regulator of the ryanodine receptor (RyR). Additionally, AD neurons showed elevated caffeine-induced mitochondrial calcium uptake, reversible by the mitochondrial calcium uniporter (MCU) blocker Ru265. RT-PCR analyses revealed downregulated insulin signaling accompanied by increased GSK3 $\beta$  expression in AD neurons. These findings support a bidirectional pathogenic feedback loop in which excessive calcium influx impairs insulin signaling, and insulin resistance further disrupts calcium homeostasis, thereby exacerbating mitochondrial dysfunction in AD. Leveraging ROSMAP's rich clinical and neuropathological data, this human iPSC derived neuronal model offers a unique platform to understand disease-relevant cellular mechanisms and opens avenues for identifying novel therapeutic targets aimed at restoring calcium homeostasis and insulin signaling in AD brain.

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**Poster**

**PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.11/C59

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

**Support:** NIH AG077103

**Title:** Synaptic and behavioral outcomes of maternal choline supplementation in a mouse model of down syndrome

**Authors:** \*E. K. WEBBER<sup>1</sup>, D. F. STEINBRENNER<sup>2</sup>, W. GALLEGOS<sup>3</sup>, M. J. ALLDRED<sup>4</sup>, S. D. GINSBERG<sup>5</sup>, G. E. STUTZMANN<sup>6</sup>;

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**Abstract:** Down syndrome (DS) is the most commonly occurring chromosomal disorder, and individuals with DS have an increased risk of developing Alzheimer's disease (AD) pathology by midlife. The hippocampus is a key area of learning and memory that is susceptible in both AD and DS. Projections from basal forebrain cholinergic neurons (BFCN) to the hippocampus are critical for memory encoding. Septohippocampal network degeneration occurs in both AD and DS, and manifests in the Ts2 [Rb (12.1716)]2Cje (Ts2) mouse model of DS. BFCN degeneration is present in the Ts2 mouse at approximately 6 months of age and coincides with cognitive decline and changes to hippocampal innervation. We hypothesize that maternal choline supplementation (MCS) can attenuate disease progression, impacting hippocampal synaptic function and learning and memory. To test this, DS mice and non-DS littermate controls (2N) of either 4-6 and 12 months of age, progeny of either choline-supplemented (CH+) or choline-normal (CHN) dams, are subjected to behavioral tests, local field potential recording electrophysiology, and western blot analysis of key synaptic proteins. Behavioral testing includes open field, Barnes maze, and marble burying to explore both anxiety-like behaviors and long-term spatial learning and memory. Acute brain slice electrophysiology assesses basal synaptic excitability, paired pulse response, and long-term potentiation, the cellular correlate of learning and memory. Western blot is used to quantify synaptophysin and PSD-95, both crucial proteins for pre- and post-synaptic function, respectively. Preliminary data show that 2N mice may respond differently to MCS than DS mice, especially in markers of presynaptic calcium availability and vesicle release, such as paired pulse response. Curiously, long-term potentiation may be attenuated by MCS in the 2N mice, with CH+ 2N mice trending toward a decrease in potentiation as compared to CHN 2N littermates. Subsequent studies are necessary to determine whether this is a normalization of hyperexcitability or a maladaptive response in a non-disease state. Thus far, our results highlight complex responses to MCS in both DS and 2N littermates

warranting further investigation into septohippocampal network function and disease progression.

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## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.12/C60

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

**Support:** NIH Grant AG077103

**Title:** Neuronal signaling and calcium alterations in mouse and human induced neurons

**Authors:** \*D. F. STEINBRENNER<sup>1,2</sup>, E. K. WEBBER<sup>2</sup>, W. GALLEGOS<sup>2</sup>, M. J. ALLDRED<sup>3</sup>, K. RAKOWIECKI<sup>4</sup>, O. LAZAROV<sup>5</sup>, S. D. GINSBERG<sup>3,6</sup>, G. E. STUTZMANN<sup>2,7</sup>;  
<sup>2</sup>Ctr. for Neurodegenerative Dis. and Therapeut., <sup>1</sup>Rosalind Franklin Univ., North Chicago, IL;  
<sup>3</sup>Nathan Kline Inst., Orangeburg, NY; <sup>4</sup>Anat. and Cell Biol., Univ. of Illinois at Chicago, Chicago, IL; <sup>5</sup>Anat. and Cell Biol., The Univ. of Illinois at Chicago, Chicago, IL; <sup>6</sup>Departments of Psychiatry and Neurosci. & Physiol. and the NYU Neurosci. Inst., New York Univ. Grossman Sch. of Med., New York, NY; <sup>7</sup>Chicago Med. Sch., North Chicago, IL

**Abstract:** By midlife, individuals with Down Syndrome (DS) will develop Alzheimer's disease (AD) pathology along with progressive cognitive decline and dementia. Basal forebrain cholinergic neurons, prefrontal cortical pyramidal neurons, and hippocampal CA1 pyramidal neurons in the septohippocampal and in the basocortical connectome are selectively vulnerable in DS individuals and display differentially expressed gene pathways in key ontology categories, including synaptic plasticity, calcium signalling, and AD-associated neurodegeneration related to beta-amyloid peptide clearance. Significant downregulation of numerous GABAergic genes and GABAergic neurotransmission pathways in DS were revealed by performing single population RNA-sequencing. To assess functional deficits, we used whole cell patch clamp electrophysiology with 2-photon (2P) Ca<sup>2+</sup> imaging within acute mouse brain slices from the Ts2 model of DS/AD to detect altered Ca<sup>2+</sup> handling and the effects in neuronal signalling. Parallel studies were conducted in iPSC-derived human neurons (HiNs) from individuals with Down syndrome (DS) and age- and sex-matched isogenic controls. Results from acute TS2 mouse brain slices compared to normal disomic (2N) littermates show altered presynaptic release properties in spontaneous postsynaptic potentials, suggesting an increased presynaptic Ca<sup>2+</sup> tone. Like in the AD mice increased resting Ca<sup>2+</sup> levels and altered pre- and postsynaptic neural signalling could be shown in HiN. Deficits in calcium handling and changes in cytosolic calcium have significant consequences in terms physiological function. These dysfunctions can be seen in animal and cellular models of DS. The above-mentioned findings provide mechanistic

information about the vulnerability of the septohippocampal and basocortical systems, leading to better outcomes in DS individuals and could show therapeutic potential for AD dementia subjects.

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## **Poster**

### **PSTR208: Alzheimer's Disease: Omics Approaches II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR208.13/C61

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

**Support:** P01AG14449  
P01AG025204

**Title:** Proteomic analysis of cognitive resilience to Alzheimer's disease pathology.

**Authors:** \*V. N. PIVTORAIKO<sup>1</sup>, E. E. ABRAHAMSON<sup>2</sup>, N. ALRAQMANY<sup>2</sup>, T. K. KARIKARI<sup>3</sup>, M. D. IKONOMOVIC<sup>2,3</sup>;  
<sup>2</sup>Neurol., <sup>3</sup>Psychiatry, <sup>1</sup>Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** Altered excitatory-inhibitory neurotransmission balance and synaptic loss result in the disconnection of neocortical circuits that underlies Alzheimer's disease (AD) dementia. Confocal microscopy analyses demonstrated differential responses of neurotransmitter-specific synapses to amyloid deposition, with densities of glutamatergic terminals reduced and gabaergic terminals preserved in areas occupied by amyloid plaques. The status of glutamate, GABA, and cholinergic receptor proteins in preclinical AD, defined as cognitively normal individuals with substantial amyloid pathology burden (also termed "cognitively resilient") is not well understood. We performed Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) analysis of synaptic proteins in frozen superior frontal cortex autopsy samples from participants in the Rush Religious Order Study with last clinical diagnosis of no cognitive impairment (NCI) or mild AD (mAD). The NCI group was divided based on neuropathology status into low-pathology (LP-NCI) and high-pathology (HP-NCI) subgroups, representative of resistance and cognitive resilience to AD pathology, respectively. Samples were fractionated using lysis buffers of different solubility strengths to extract soluble/diffusible (PBS) and membrane-associated (Na<sub>2</sub>CO<sub>3</sub>) proteins. ANOVA tests were used to select features with significant diagnostic group difference within each fraction. Compared to LP-NCI, total A $\beta$  peptides were higher in HP-NCI and mAD, in both fractions. The HP-NCI group was uniquely characterized by a robust upregulation of TIMP3, an inhibitor of metalloproteinases that promotes amyloidogenesis, in the soluble fraction. Compared to the LP-NCI (resistant) group, we found evidence of early upregulation of NMDA R1, but not AMPA R3, as well as GABA-B R1 and GABA-A g2

proteins and trends for upregulation of mAChR M1 protein in the PBS diffusible fraction from HP-NCI (resilient) and AD groups. Levels of synaptogyrin-2 were stable in HP-NCI, suggestive of a preserved synaptic plasticity, and reduced in mAD. LP-NCI, HP-NCI, and mAD groups did not differ by the examined proteins in membrane associated fraction. The robust upregulation of TIMP3 in HP-NCI group could be responsible for the significant amyloid burden in cognitively normal elderly people; this could be an initial protective mechanism whereby higher levels of soluble A $\beta$  forms are sequestered into inert accumulates. The observed increases in receptor proteins from the soluble fraction could be due to higher abundance of selected proteins or impediments in their delivery and incorporation into cell membranes in preclinical and early AD.

**Disclosures:** V.N. Pivtoraiko: None. E.E. Abrahamson: None. N. Alraqmany: None. T.K. Karikari: None. M.D. Ikonomic: None.

## Poster

### PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.01/Web Only

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

**Support:** AMED Grant JP20dm0207001  
JSPS KAKENHI 24K18633  
JSPS KAKENHI 23H02097

**Title:** Impaired neprilysin-mediated amyloid- $\beta$  degradation contributes to Alzheimer's disease pathogenesis

**Authors:** \*T. MORITO, T. C. SAIDO;

Lab. for Proteolytic Neurosci., RIKEN Ctr. for Brain Sci., Wako-shi, Saitama, Japan

**Abstract:** Amyloid- $\beta$  (A $\beta$ ) peptide deposition in the brain is considered a key initiating factor in the development of Alzheimer's disease (AD). Age-related decline in neprilysin (NEP), a major A $\beta$ -degrading enzyme, has been implicated in the pathogenesis of sporadic AD by promoting A $\beta$  accumulation. We previously demonstrated that A $\beta$  degradation is significantly impaired in the *App* knock-in mouse model (*App*<sup>NL-G-F</sup>) when NEP or insulin-degrading enzyme (IDE) is genetically ablated. Notably, A $\beta$  deposition was more pronounced in NEP-deficient mice than in IDE-deficient mice, and the combined deletion of both enzymes synergistically exacerbated A $\beta$  pathology (Morito T, et al., *J Neurosci*, 2025). We further examined an AD-associated NEP mutation that results in an M8V amino acid substitution located in the intracellular domain, rather than the catalytic extracellular domain. This variant impairs NEP's ability to degrade extracellular A $\beta$  by altering its cellular localization through enhanced phosphorylation of intracellular serine residues in SH-SY5Y human neuroblastoma cells. These findings support the hypothesis that NEP dysfunction may contribute causally to AD pathogenesis. In this

presentation, we will discuss the extent of NEP's involvement in AD etiology and explore strategies to restore or enhance its activity as a potential therapeutic approach.

**Disclosures:** T. Morito: None. T.C. Saido: Other; RIKEN BIO Co. Ltd..

## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.02/C62

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

**Title:** Synaptotagmin1 directly interacts with BACE1 and promotes its lysosomal degradation

**Authors:** \*T. WADA<sup>1</sup>, S. UEDA<sup>1</sup>, K. GOTO<sup>2</sup>, M. AKAHORI<sup>1</sup>, C. HONJO<sup>1</sup>, M. MATSUMOTO<sup>1</sup>, R. TAKAHASHI<sup>3</sup>, R. MATSUMOTO<sup>1</sup>, A. KUZUYA<sup>1</sup>;

<sup>1</sup>Dept. of Neurol., <sup>2</sup>Dept. of Regulation of Neurocognitive Disorders, Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; <sup>3</sup>Office of Res. Acceleration, Kyoto Univ., Kyoto, Japan

**Abstract:** Background and aims: Amyloid  $\beta$  peptide ( $A\beta$ ) plays a pivotal role in the synaptic dysfunction of Alzheimer's disease (AD). While  $\beta$ -site APP cleaving enzyme 1 (BACE1) cleaves amyloid precursor protein (APP) to initiate  $A\beta$  production, the precise mechanisms regulating BACE1 activity at synapses remain poorly understood. Synaptotagmin1 (Syt1), a major synaptic vesicle protein, regulates  $A\beta$  production through interactions with APP and presenilin-1, the catalytic subunit of  $\gamma$ -secretase. However, a potential interaction between Syt1 and BACE1 remains unknown. This study investigated whether Syt1 interacts with and regulates BACE1. Methods: HEK 293 cells were co-transfected with the plasmids expressing BACE1 and either Syt1 or an empty vector as control. 24 hours after transfection, conditioned media were replaced, and cells and conditioned media were collected after an additional 12 hours. Western blotting assessed BACE1 expression in soluble lysates, while co-immunoprecipitation (Co-IP) analyzed Syt1-BACE1 interactions. ELISA quantified sAPP $\alpha$  and sAPP $\beta$  levels in conditioned media (n=6). MIN6 cells transfected with Syt1 or control were analyzed for endogenous BACE1 expression (n=8). To investigate the effect of Syt1 on BACE1 degradation, Syt1-transfected MIN6 cells were treated with chloroquine (CQ), a lysosomal inhibitor, followed by Western blot analysis (n=6). Results: Co-IP confirmed a novel Syt1-BACE1 interaction. Co-overexpression of Syt1 and BACE1 in HEK 293 cells significantly reduced both BACE1 protein levels and sAPP $\beta$  secretion, while sAPP $\alpha$  levels remained unchanged. Single transfection of Syt1 significantly reduced endogenous BACE1 levels in MIN6 cells. Furthermore, CQ treatment increased the BACE1 increasing ratio in Syt1-transfected cells, indicating Syt1 promotes BACE1 lysosomal degradation. Conclusion: Syt1 downregulates amyloidogenic processing of APP by directly facilitating lysosomal degradation of BACE1. Previous studies have demonstrated that Syt1 expression levels are reduced in AD brains, while BACE1 expression levels are increased. We hypothesize that reduced Syt1 expression results in impaired lysosomal degradation, leading to elevated BACE1 expression levels in AD.

**Disclosures:** T. Wada: None. S. Ueda: None. K. Goto: None. M. Akahori: None. C. Honjo: None. M. Matsumoto: None. R. Takahashi: None. R. Matsumoto: None. A. Kuzuya: None.

**Poster**

**PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.03/C63

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

**Support:** NIH Grant AG067832

**Title:** Advancing Alzheimer's disease animal modeling: intrathecal administration of amyloid-beta oligomers (ABOs) and changes in pTau 12 months post ABOs in primates

**Authors:** \*M. R. WEED<sup>1</sup>, R. BOUFFARD<sup>2</sup>, J. D. ELSWORTH<sup>2</sup>, E. RAMIREZ<sup>2</sup>, M. MILES<sup>2</sup>, R. DANGE<sup>2</sup>, I. CASTRO COLMENARES<sup>2</sup>, M. LAWRENCE<sup>2</sup>;  
<sup>1</sup>CNS, <sup>2</sup>Virscio, Inc, New Haven, CT

**Abstract:** Alzheimer's disease (AD) is the most common form of dementia and was estimated in 2024 to account for 60-80% of dementia cases (Alzheimer's Association, 2024 Alzheimer's disease facts and figures). The lack of effective treatments to stem the progression of AD signifies a need for improved preclinical test systems and animal models. Strong evidence indicates that in AD, amyloid beta oligomers (AβOs) play a major role in initiating a pathological cascade in brain that includes induction of phosphorylated tau (p-tau), neurofibrillary tangles, amyloid plaques, loss of synapses and neurons, neuroinflammation, and the clinical manifestation of cognitive decline. The current study assessed to what extent repeated administration of AβOs to adult African green monkeys through a subcutaneous access port into the lumbar intrathecal CSF models AD pathology. We have previously demonstrated this regimen to induce some aspects of AD-like pathology in green monkeys, including increasing brain p-tau / AT8 staining for up to 3 months after delivery. The present study includes immunohistochemical data from additional cohorts of green monkeys examined up to 12 months after AβO administration. We determined that repeated IT administration of AβOs to young adult NHPs increases characteristics of AD-like pathology in key neuroanatomical regions implicated in AD. Notably, elevated expression of p-tau in the medial temporal cortical memory circuit (e.g., hippocampus and entorhinal cortex) detected by AT8 immunostaining persisted for at least 8 months after AβO delivery. The effects of AβOs on p-tau is being investigated at 12 months after administration to assess the duration and extent of AD-like pathology. The goal of this nonhuman primate (NHP) model is to determine pathways of AD-like pathology induced by AβOs in African green monkeys. Elucidating these pathways in a NHP model should enable development of novel therapeutics for AD in a manner that significantly de-risks clinical trials.

**Disclosures:** M.R. Weed: A. Employment/Salary (full or part-time): Virscio, Inc. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and



pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH AG067832. **R. Bouffard:** A. Employment/Salary (full or part-time): Virscio, Inc. **J.D. Elsworth:** A. Employment/Salary (full or part-time): Virscio, Inc. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH AG067832. **E. Ramirez:** A. Employment/Salary (full or part-time): Virscio, Inc. **M. Miles:** A. Employment/Salary (full or part-time): Virscio, Inc. **R. Dange:** A. Employment/Salary (full or part-time): Virscio, Inc. **I. Castro Colmenares:** A. Employment/Salary (full or part-time): Virscio, Inc. **M. Lawrence:** A. Employment/Salary (full or part-time): Virscio, Inc. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH AG067832.

## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.04/C64

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

**Support:** Psychiatry in Southern Region of Denmark, Mental Service Hospital  
Independent Research fund, Southern Region of Denmark

**Title:** Age-associated alterations in glucose metabolism and amyloid plaque accumulation in AD signature regions of healthy individuals

**Authors:** \***M. SEYEDI VAFAEE**<sup>1,2</sup>, L. KNUDSEN<sup>2</sup>, T. MICHEL<sup>2</sup>;  
<sup>1</sup>Psychiatry Res. Unit, <sup>2</sup>Univ. of Southern Denmark, Odense, Denmark

**Abstract: Purpose:** Decrease in neurogenesis, increase of mitochondrial malfunction, and as a result, impaired energy metabolism and increase of beta amyloid (A $\beta$ ) plaques are held to be key mediators of aging and age-related neurological disorder such as dementia and AD. We aimed to investigate the interplay between cerebral glucose metabolism, and increased A $\beta$  plaques and its effect on grey matter density and white matter integrity during the process of aging.

**Methods:** Ninety healthy subjects between 20-80 years underwent one <sup>11</sup>C-PiB and one <sup>18</sup>F-FDG PET scans and a series of simultaneous MRI scans including arterial spin labeling (ASL) and diffusion tensor imaging (DTI) scans for the measurement of cerebral blood flow (CBF) and white matter integrity (WMI) accordingly.

**Results:** We found a positive correlation between A $\beta$ -deposition and aging, and a negative correlation between glucose metabolism and aging. The insula showed the strongest negative correlation between glucose metabolism and age (Spearman's  $r = -0.683$ , 95% CI [-0.79, -0.54],  $p < 0.0001$ ), while the posterior cingulate cortex had the strongest positive correlation between A $\beta$ -deposition and age (Spearman's  $r = 0.479$ , 95% CI [0.28, 0.64],  $p < 0.0001$ ). These results

suggest a spatially dependent link between A $\beta$ -deposition and metabolism in healthy older adults, indicating a compensatory mechanism in early AD. Additionally, A $\beta$ -deposition was linked to changes in interregional neural communication.

**Conclusions** Our study confirms previous findings on aging and offers new insights, particularly on the role of A $\beta$ -deposition in healthy aging. We observed a linear increase in A $\beta$ -deposition, alongside decreases in white matter integrity, cerebral blood flow, and glucose metabolism. Additionally, we identified a complex regional relationship between A $\beta$ -deposition, glucose metabolism, and neural communication, reflecting a compensatory mechanism.

**Disclosures:** M. Seyedi Vafae: None. L. Knudsen: None. T. Michel: None.

## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.05/D1

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

**Title:** The role of Y132- in Tyrosine-Kinase dependent suppression of homomeric Kv1.2: Implications for Alzheimer's Disease

**Authors:** \*D. JAMSHIDI<sup>1</sup>, J. HYATT<sup>1</sup>, S. BURCH<sup>2</sup>, N. RANGINWALA<sup>1</sup>, T. YAKLIN<sup>1</sup>, J. FARLEY<sup>3</sup>;

<sup>1</sup>Indiana Univ., Bloomington, IN; <sup>2</sup>Indiana Univ. Bloomington, Bloomington, IN; <sup>3</sup>Neurosci., Indiana Univ. Program in Neurosci., Bloomington, IN

**Abstract:** The roles of A $\beta$  in the pathogenesis of Alzheimer's disease (AD) includes disruption of synaptic communication/function and synaptic plasticity mechanisms thought to underlie learning and memory. Exactly how these abnormal processes arise is not fully understood, but evidence suggests that dysregulation of intracellular Ca<sup>2+</sup> levels is involved in alterations of neuronal excitability, synaptic remodeling, and neurodegeneration in AD. Our lab has focused on the potential involvement of voltage-gated potassium channels (VGKCs) in these processes, particularly Kv1.x family members as they regulate Ca<sup>2+</sup> influx, and their inhibition may lead to synapto- and neurotoxicity through hyperexcitability and excess glutamate release. We have previously observed rapid and robust suppression (~50% in 30 min) of macroscopic current by A $\beta$ (1-42) in homomeric Kv1.1, Kv1.2, and heteromeric Kv1.1/1.2 channels. The Ca<sup>2+</sup> chelator BAPTA-AM and PP2B inhibitor Cyclosporin A (CsA) both reduced A $\beta$ -suppression to ~20%. In contrast, the broad spectrum PTK inhibitor genistein completely eliminated suppression by A $\beta$ (1-42) indicating a role for endogenous PTKs in A $\beta$ -suppression. Thus we sought to understand the role of residue Y132 in the suppression by A $\beta$  and whether PYK2, a PTK known to suppress Kv1.2 acts upon this residue. To test this, we generated the Y132F mutant from a WT KV1.2-pGEMHE plasmid using a PCR-based site-directed mutagenesis kit (NEB). *In vitro* transcription reactions were utilized to generate both mutant and WT cRNAs. The PYK2-pGH19 plasmid was provided by Professor Johannes Hell lab (University of California, Davis). Stage

V/*VI X. laevis* oocytes were injected with ~1ng of WT Kv1.2 or Y132F cRNA, in addition to PYK2 cRNA. Effects of bath application of 1  $\mu$ M of A $\beta$ (1-42) were evaluated using TEVC electrophysiology with recordings obtained 24-48 hrs post cRNA-injections. Baseline currents were unaffected by the Y132F mutant compared to WT controls, with no difference in control recordings in response to DMSO solvent (n=15, p > 0.05). Co-expression of PYK2 with Kv1.2 Y132F resulted in significantly less current suppression than co-expression of PYK2 with WT Kv1.2 (n=8, p > 0.02). Additionally, Y132F channels exhibited greater resistance to suppression by A $\beta$ (1-42), with 17% suppression (n=10) compared to the ~50% suppression for WT channels 30 minutes post exposure (n=10, p < 0.007). Phosphorylation at site Y132, via PYK2 or other candidate PTKS, may be a critical mediator of A $\beta$  based suppression of Kv1.2 current, particularly through endocytotic methods. Suppression of these channels may lead to increased excitotoxicity via excess Ca<sup>2+</sup> influx and glutamate release.

**Disclosures:** D. Jamshidi: None. J. Hyatt: None. S. Burch: None. N. Ranginwala: None. T. Yaklin: None. J. Farley: None.

## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.06/D2

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

**Support:** Nu Rho Psi Undergraduate Research Grant  
NIH R56-MH130488  
Sloan Research Fellowship

**Title:** Evaluating the role of amyloid beta in cognitive deficits using 5xFAD mice

**Authors:** \*N. IMOMDODOVA<sup>1</sup>, S. KORDE<sup>2</sup>, E. HWANG<sup>3</sup>;

<sup>1</sup>Lake Forest Col., Lake Forest, IL; <sup>2</sup>Rosalind Franklin Univ. of Med. and Science, Chicago Med. Sch., Park City, IL; <sup>3</sup>Chicago Med. Sch., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

**Abstract:** Alzheimer's disease (AD) is characterized by the accumulation of amyloid-beta (A $\beta$ ) plaques and tau tangles, leading to progressive cognitive decline. The 5xFAD mouse model, which carries five familial AD mutations, is widely used to study early-onset AD pathology. While this model reliably exhibits early and robust A $\beta$  deposition, the onset and severity of cognitive deficits and their relationship to plaque accumulation remain poorly understood. As plaque formation starts in early stages of AD, the associated cognitive deficits might be subtle and become evident only in highly complex cognitive tasks. Thus, in this study, we employed the International Brain Laboratory (IBL) task—a complex, multifaceted behavioral assay that assesses learning, memory, sensory processing, exploratory behavior, and decision-making—to evaluate cognitive function and investigate its correlation with A $\beta$  plaque deposition.

Specifically, in the IBL task, mice learn to discriminate between two visual stimuli and report the stimulus identity by turning a steering wheel in opposite directions. The task was administered to 5xFAD and wild-type mice in two age groups (2 months and 5-7 months) over a one-month period. Remarkably, despite substantial plaque burden, 5xFAD mice performed comparably to age-matched controls: long-term learning curves, initial exploratory behavior, and age-related decline did not differ between groups. These findings highlight the limitations of using A $\beta$  pathology alone to predict cognitive outcomes in 5xFAD mice. Instead, the predominant role of A $\beta$  may be permissive or modulatory, potentially facilitating downstream processes, such as tau pathology, neuroinflammation, and neurodegeneration, that ultimately drive cognitive deficits.

**Disclosures:** N. Imomdodova: None. S. Korde: None. E. Hwang: None.

## Poster

### PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.07/D3

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

**Support:** NIH Grant AG076921

**Title:** Rare PICALM coding mutation H458R (murine H465R) protects against amyloid-beta pathology in a murine 5xFAD model

**Authors:** \*K. KISLER<sup>1</sup>, Z. DAI<sup>1</sup>, A. P. SAGARE<sup>2</sup>, A. GROND<sup>2</sup>, B. ZLOKOVIC<sup>2</sup>, M. P. COBA<sup>1</sup>;

<sup>2</sup>Physiol. and Neurosci., <sup>1</sup>USC, Los Angeles, CA

**Abstract:** *PICALM* is a highly validated genetic risk factor for late-onset Alzheimer's disease (LOAD). Reduced *PICALM* expression has been associated with LOAD progression. *PICALM* is a chaperone protein involved in clathrin-mediated endocytosis and amyloid clearance, but its role in disease progression is not well understood. GWAS and meta-analyses studies have revealed several rare coding variants of *PICALM* associated with LOAD, including *PICALM* H458R. AAV expression of murine *PICALM* H465R, the murine equivalent to human H458R, in cultured primary mouse *Picalm*<sup>-/-</sup> neurons revealed greater protection against amyloid-beta oligomer (A $\beta$ o) toxicity than wildtype *PICALM*. Mice expressing *PICALM* H465R crossed to 5xFAD Alzheimer's disease (AD) model mice (*Picalm*<sup>R/R</sup>; 5xFAD) showed improved performance on behavioral tests, and less neuron loss in cortex layer 5 compared to control *Picalm*<sup>H/H</sup>; 5xFAD mice at 9 months of age. Interestingly, pan-A $\beta$  staining in cortex and hippocampus did not reveal differences in amyloid load between *Picalm*<sup>R/R</sup>; 5xFAD and *Picalm*<sup>H/H</sup>; 5xFAD mice at 9 mo, implying *Picalm*<sup>R/R</sup>; 5xFAD mice were more resilient to amyloid pathology. Returning to our neuronal culture model, we found that *PICALM* H465R exhibits an affinity for proteins involved with the protective unfolded protein response (UPR) pathway, upregulating a pro-adaptive signaling cascade to maintain ER homeostasis and protect

against A $\beta$  toxicity. This data reveals a new role for PICALM and indicates that PICALM H465R protection may be due to enhanced binding affinity to UPR proteins.

**Disclosures:** K. Kisler: None. Z. Dai: None. A.P. Sagare: None. A. Grond: None. B. Zlokovic: None. M.P. Coba: None.

## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.08/D4

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

**Support:** NIH NIA 1RF1-AG079185

**Title:** Cell-autonomous deposition of fibrillar amyloid plaque cores in living neurons

**Authors:** \*C. G. GLABE;

Mol. Biol. and Biochem., Univ. California Irvine, Irvine, CA

**Abstract:** The mechanisms of amyloid plaque core deposition are incompletely understood. We analyzed the cellular dynamics of Abeta amyloid plaque core formation by labeling the proteome of specific cell populations using the Cre-specific expression of an engineered methionyl tRNA synthetase (MetRS\*) to facilitate the incorporation of azidonorleucine (ANL) at AUG codons. We expressed MetRS\* in 3 different populations of neurons, astrocytes and microglia in 5XFAD and APP<sup>SAA</sup> mouse models of plaque formation. At the earliest times of plaque formation in 5XFAD, 6 weeks, the smallest methoxy XO4 (MXO4) and thioflavin S (ThS) staining “fibrillar” plaque cores are 3-5 um and contained wholly within NeuN staining neuronal nuclei and colocalize with chromatin. After 48 hr pulse labeling of 6 wk CamK-Cre MetRS expressing 5XFAD mice with ANL followed by fluorescent detection of the ANL-labeled protein with Cu-mediated click reaction with Alexa647 alkyne, we found that newly synthesized ANL-containing protein is only detected in the nuclei of neurons expressing MetRS\* and that nascent plaque cores in adjacent MetRS\* negative neurons show no evidence of ANL-labeled protein. In larger 10 - 30 um plaque cores, the MXO4 and ThS positive cores colocalize with chromatin-staining dyes, like DAPI, but the NeuN-staining material is fragmented and peripheral to the core. At 8 wk, approximately 12% of nascent plaque cores are ANL+, comparable to the fraction of neurons expressing MetRS\*, while at later times the fraction of ANL+ cores drops to 4% at 12 wk and remains constant until 25 wk, suggesting that the rate of plaque core formation remains constant over this period as the number of plaques increases. At these later times there is no evidence of transfer of ANL-labeled protein to cores that do not express MetRS\*, but we find that ANL-labeled newly synthesized protein is transferred to vascular amyloid over the same period, suggesting that this process is not cell autonomous. Similar results were obtained with CamK-Cre APP<sup>SAA</sup> mice. Upon labeling of astrocyte and microglia Cre-expressing MetRS\* 5XFAD lines continuously for 4-5 months, we observed cell autonomous transfer of ANL-

labeled astrocyte protein to plaque cores surrounded by MetRS\*-expressing astrocytes, but no ANL labeled protein was observed to be transferred from microglia to the core even though Iba1 labeled microglial process extensively invade the cores. These results indicate that the initial deposition and growth of plaque cores occurs inside single living neurons. Supported by NIH NIA 1RF1-AG079185.

**Disclosures:** C.G. Glabe: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AltPep Corp.

## Poster

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.09/D5

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

**Title:** Lysosome-targeting acidic nanoparticles restore lysosomal acidification and mitigate amyloid-induced neurotoxicity in Alzheimer's disease models

**Authors:** \*N. DONG<sup>1</sup>, D. MURPHY<sup>2</sup>, K. KALARY<sup>2</sup>, A. M. BARRON<sup>3</sup>, J. ZENG<sup>2</sup>, C. LO<sup>1</sup>;  
<sup>1</sup>Biol., <sup>2</sup>Syracuse Univ., Syracuse, NY; <sup>3</sup>Nanyang Technological Univ., Singapore, Singapore

**Abstract:** Alzheimer's disease (AD) is characterized by the progressive accumulation of misfolded proteins, notably amyloid-beta 42 (A $\beta$ 42), which disrupts neuronal function and leads to cognitive decline. Lysosomal alkalization impedes autophagic clearance of toxic aggregates, exacerbating pathology. Here, we investigate the therapeutic potential of lysosome-targeting acidic nanoparticles (AcNPs) in restoring lysosomal acidification and rescuing neuronal dysfunction in amyloid-driven models of AD. A $\beta$ 42 oligomer treatment in SH-SY5Y cells induces lysosomal alkalization, mitochondrial dysfunction, and impaired autophagy, providing a tractable in vitro model to evaluate how AcNPs may reverse these pathological changes through lysosomal restoration. Our data support the role of AcNPs in re-acidifying lysosomes and improving cellular functions under A $\beta$ 42-induced stress conditions. To further validate these findings in vivo, we analyzed wild-type and APP knock-in (APP-KI) mice at distinct ages, representing key stages of disease progression. Western blot profiling across brain tissues revealed consistent downregulation of lysosomal vacuolar (H<sup>+</sup>)-ATPase (V-ATPase) subunits and mitochondrial respiratory chain proteins, and increased accumulation of autophagosomal protein. These alterations, which reflect disrupted lysosomal acidification, mitochondrial dysfunction, and autophagic clearance associated with A $\beta$ 42 pathology in the APP-KI mice, were partially reversed by AcNP treatment. Additionally, in APP-KI mice, we observed increased levels of pro-inflammatory cytokines and activation of necroptotic signaling proteins (e.g., MLKL and RIPK3), which are known mediators of programmed cell death. These pathological changes were attenuated following AcNP treatment, suggesting that targeting lysosomal function may also alleviate inflammation and death-related signaling triggered by A $\beta$ 42 accumulation. In conclusion, these findings suggest that AcNPs act through effective

targeting of lysosomes to restore their acidification and degradative capacity, enhancing autophagy, promoting mitochondrial turnover, and facilitating clearance of A $\beta$ 42. These effects together contribute to the reduction of neuroinflammation and neurodegeneration associated with A $\beta$ 42 pathology. Our preliminary data support a novel therapeutic paradigm in which targeted re-acidification of lysosomes using AcNPs counteracts A $\beta$ 42-mediated lysosomal and neuronal damage. AcNPs hold promise both as a research tool for lysosomal biology and as a potential therapeutic for AD in the future.

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## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.10/D6

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

**Support:** NRF Grant RS-2022-NR070151  
NRF Grant RS-2024-00402116  
MOTIE Grant RS-2024-00419358

**Title:** Behavioral analysis of dementia with hearing loss in rat animal model

**Authors:** \*Y. PARK<sup>1</sup>, J. PARK<sup>1</sup>, D. CHOI<sup>4</sup>, N. SHIN<sup>4</sup>, S. HWANG<sup>1</sup>, M. CHANG<sup>5</sup>, J. SUNG<sup>2</sup>, M. PARK<sup>4</sup>, S. JUN<sup>1,3</sup>;

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**Abstract:** Hearing loss has emerged as a significant and modifiable risk factor for dementia. Importantly, auditory function can often be restored through rehabilitation devices such as hearing aids and cochlear implants. Therefore, elucidating the causal relationship between hearing loss and cognitive decline is essential for developing effective preventive strategies against dementia. However, the underlying pathological mechanisms remain unclear, and experimental evidence from preclinical models is limited. Moreover, auditory deprivation may accelerate cognitive deterioration via indirect pathways, including social isolation and depression. To address these issues, we established a rodent model combining noise-induced hearing loss with low-dose amyloid- $\beta$  infusion to evaluate their synergistic effects on cognitive behavior. Animals were divided into four experimental groups based on auditory and amyloid exposure: control, noise-induced hearing loss only, amyloid- $\beta$  only, and combined exposure. Cognitive function was assessed using the Y-maze and Barnes maze tasks to evaluate working memory, spatial learning, and cognitive flexibility. Behavioral data were quantitatively analyzed

using video-based tracking software. Our results revealed that rodents subjected to combined exposure exhibited significantly greater cognitive impairment than those in either single-condition group, particularly during task phases requiring strategy shifts and environmental adaptation. These findings highlight the critical role of auditory input not only in sensory processing but also in supporting higher-order cognitive functions, underscoring the importance of early auditory intervention in dementia prevention.

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## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.11/D7

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

**Support:** CSIR-UGC

**Title:** Therapeutic Potential of 6BIO and DKK1-LRP6 Inhibitor in Wnt/ $\beta$ -Catenin Pathway Modulation for A $\beta$ -Induced Alzheimer's Disease model

**Authors:** \*M. PRAJAPAT<sup>1</sup>, P. SARMA<sup>2</sup>, A. PRAKASH<sup>3</sup>, B. MEDHI<sup>4</sup>;  
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**Abstract:** The Wnt/ $\beta$ -catenin signaling pathway plays a crucial role in CNS development, with emerging evidence linking its dysregulation to the progression of Alzheimer's disease (AD). This study investigates the activation of Wnt signaling by targeting GSK3 $\beta$  and the DKK1/LRP6 interaction using a combination of 6BIO (6Bromoindirubin-3-oxime) and a novel gallocyanine derivative (8e) modulator. This combination strategy represents the first comprehensive attempt to address Wnt signaling dysregulation in AD by simultaneously targeting both intracellular and extracellular regulatory mechanisms. We identified the effects of 6BIO (10 $\mu$ M) and 8e (20 $\mu$ M) were assessed in SH-SY5Y cells treated with A $\beta$ 1-42 (20 $\mu$ M). The efficacy of these modulators was also evaluated in male Wistar rats through dose-ranging studies. An Alzheimer's disease model was established via intracerebroventricular injection of A $\beta$ 1-42, followed by treatment with 6BIO (23.8  $\mu$ g/kg/day, i.p.) and 8e (4.2 mg/kg/day, i.p.). In Amyloid beta (A $\beta$ 1-42) treated SHSY5Y cells, 6BIO and 8e significantly reduced ROS production and apoptotic activity while modulating protein expression. *In-vivo* study, rats treated with the combination of 6BIO and 8e exhibited improved neurobehavioral activity compared to AD model rats, along with altered expression of DKK1,  $\beta$ -catenin, p-tau, and pGSK3 $\beta$ . Additionally, decreased oxidative stress and apoptosis markers. These findings suggest that the combined targeting of GSK3 $\beta$  and LRP6



represents a promising therapeutic strategy for AD. The combination of 6BIO and 8e shows potential as a novel modulator and warrants further investigation in clinical trials to assess its therapeutic efficacy.

**Disclosures:** M. Prajapat: None. P. Sarma: None. A. Prakash: None. B. Medhi: None.

## Poster

### PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.12/D8

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

**Support:** AMED Grant JP25wm0625001

**Title:** Investigation of the effects of APOE rare variants on Abeta oligomers

**Authors:** \*T. HASHIMOTO<sup>1</sup>, N. FUJIKAKE<sup>1</sup>, A. OBINATA<sup>2</sup>, T. IKEUCHI<sup>2</sup>, A. MIYASHITA<sup>2</sup>;

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**Abstract:** Apolipoprotein E (apoE), encoded by the *APOE* gene, plays a critical role in brain lipid homeostasis, including lipid transport and the redistribution of lipid droplets. There are three common alleles of the human *APOE* gene:  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ . Among these, the *APOE*  $\epsilon 4$  allele is the strongest genetic risk factor for the onset of Alzheimer's disease (AD). Recently, several rare missense variants of *APOE* gene have also been reported to be associated with AD. The *Christchurch* variant (R136S) has been shown to suppress AD onset in a familial AD pedigree linked to the *PSEN1* gene. Similarly, the *Jacksonville* variant (V236E) has been identified as a protective allele in AD cohorts from the United States and the United Kingdom, while the *APOE*  $\epsilon 5$  (E3K) and  $\epsilon 7$  (EE244/245KK) alleles have been reported as protective in Japanese cohort. However, the molecular mechanisms whereby these *APOE* rare missense variants influence AD onset remain largely unknown. It has been reported that apoE modulates the levels of A $\beta$  oligomers in the brain in an allele-dependent manner. To investigate the role of apoE in A $\beta$  oligomer formation, we employed a recently developed bi-luminescence complementation (BiLC) assay. In this assay, the N- and C-terminal fragments of *Gaussia* luciferase are separately fused to the N-terminus of A $\beta$ 1-42. When split-luciferase-tagged A $\beta$  forms oligomers, the luciferase fragments are brought into proximity and reconstitute a functional molecule that exhibits luminescence. Using the BiLC assay to monitor A $\beta$  oligomerization, we found that both apoE3 and apoE4 increased the luminescence compared to mock-transfected controls, with apoE4 showing a significantly greater effect than apoE3. Furthermore, apoE3-EE244/245KK ( $\epsilon 7$  allele) exhibited a significant increase in luminescence compared to apoE3, while apoE3-V236E (*Jacksonville* variant) showed a trend toward decreased luminescence. In contrast, apoE3-R136S (*Christchurch* variant) and apoE3-E3K ( $\epsilon 5$  allele) exhibited luminescence levels comparable to

that of apoE3. These findings suggest that *APOE*  $\epsilon 4$  may contribute to AD pathogenesis by promoting A $\beta$  oligomerization. Notably, both the  $\epsilon 7$  allele and the *Jacksonville* variant are located near the lipid-binding domain of apoE, suggesting that this region may be critical for the apoE-mediated modulation of A $\beta$  oligomerization. Further investigation of how structural changes in apoE caused by rare variants affect A $\beta$  oligomerization may provide key insights into the role of apoE in the onset of AD.

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## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.13/D9

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

**Title:** Thiamine Supplementation Ameliorates Hif1 $\alpha$  -Mediated Toxicity From AB1-42

**Authors:** \*Y. T. ANDERSON<sup>1</sup>, B. BLACKBURN<sup>1</sup>, S. JAHAN<sup>2</sup>, J. ZASTRE<sup>3</sup>;  
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**Abstract:** Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by an accumulation of neurofibrillary tangles and amyloid beta plaques in the brain. Existing therapeutics, while effective at slowing the progression of these characteristics, do not target the neurotoxicity resulting from plaque and tangle formation. Hypoxia Inducible Factor-1 $\alpha$  is a driver of many neurotoxic pathways and has been shown to be activated in response to A $\beta$ . We have previously identified HIF1 $\alpha$  as an upstream mediator promoting AD-like pathology driven by thiamine (vitamin B1) deficiency. Thiamine supplementation has garnered growing interest as a treatment for AD, ameliorating A $\beta$ -induced neurotoxicity, but the mechanism underlying these protective effects is unclear. The objective of this work is to elucidate the mechanism(s) that may be involved in thiamine's protective effects against A $\beta$ . We hypothesize that the therapeutic effects of thiamine supplementation may be mediated through the modulation of HIF1 $\alpha$  activity, thereby attenuating A $\beta$ -induced apoptosis. We utilized an in vitro model of amyloid toxicity using N2A neuronal cells treated with A $\beta$ <sub>1-42</sub> in the presence or absence of thiamine. Thiamine demonstrated significant protection against A $\beta$ <sub>1-42</sub>-induced toxicity, enhancing viability and reducing apoptosis, as indicated by a decrease in cleaved caspase 3 expression. Thiamine achieved this protection against apoptosis through two independent pathways. First, it significantly reduced mitochondrial BNIP3 dimerization, thereby improving mitochondrial membrane potential and mitigating the release of cytochrome C into the cytosol. Additionally, thiamine supplementation suppressed endoplasmic reticulum (ER) stress by reducing A $\beta$ <sub>1-42</sub>-induced expression of GRP78, ATF4, and CHOP. To further investigate the relationship between amyloid accumulation and HIF1 $\alpha$ -mediated toxicity in vivo, we utilized female 3xTg-AD and wild-type (WT) mice aged 6, 12, and 18 months. As the amyloid burden increased with age in

3xTg-AD mice, we observed a corresponding rise in apoptotic markers, such as BNIP3, and elevated ER stress. Our findings suggest that thiamine supplementation protects against A $\beta$ <sub>1-42</sub> by reducing HIF1 $\alpha$ -mediated toxicity through reductions in BNIP3 dimerization, mitigating cytochrome C release, and attenuating ER stress. This identifies HIF1 $\alpha$  inhibition as the crucial molecular target underlying the beneficial role of thiamine supplementation in AD treatment.

**Disclosures:** Y.T. Anderson: None. B. Blackburn: None. S. Jahan: None. J. Zastre: None.

## Poster

### PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.14/D10

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

**Support:** James Fickel Alzheimer's Disease Research Fund (XF)  
NIH/R01EY028158 (XF)  
NIH/R01EY032488 (XF)

**Title:** Synergistic Induction of Neuronal-Like Cell Death by Extracellular beta-Amyloid and Intracellular Glutathione Deficiency via Ferroptosis

**Authors:** \*K. RADEEN, C. HAO, Z. WEI, K. LI, X. FAN;  
Cell. Biol. and Anat., Med. Col. of Georgia at Augusta Univ., Augusta, GA

**Abstract:** Alzheimer's Disease (AD) is a progressive neurodegenerative condition marked by the presence of amyloid-beta (A $\beta$ ) plaques and neurofibrillary tangles, with aging recognized as the primary risk factor. Oxidative stress, which accumulates with age, is believed to play a critical role in the development of AD and other neurodegenerative diseases. Glutathione (GSH), the brain's most prevalent antioxidant, declines with age and is further depleted in individuals with AD and dementia. However, the precise molecular role of GSH in brain aging and AD remains unclear. This study aimed to investigate neuronal-like cell death under conditions that mimic brain aging. SH-SY5Y cells were either treated with synthetic  $\beta$ -amyloid oligomers or induced to overexpress wild type or mutated (APP<sub>SW/Ind</sub>) amyloid precursor protein (APP). Levels of A $\beta$ <sub>1-42</sub> and A $\beta$ <sub>1-40</sub> were quantified using ELISA and western blot. Intracellular GSH synthesis was disrupted by inhibiting GCLC activity with buthionine sulfoximine (BSO) or dimethyl fumarate (DMF). Cell viabilities were evaluated through cell morphology imaging and the cell counting kit-8 (CCK8). The mechanisms of cell death were evaluated and lipid peroxidation was monitored by using C11-BODIPY and 4-HNE staining and blotting. Treatment of APP<sub>SW/Ind</sub> overexpressing SHSY5Y cells with 350 $\mu$ M of BSO for 46 hours reduced cell viability to 25%, which was rescued to 85% by the lipid peroxidation inhibitors liproxstatin I and ferrostatin I. Similarly, SH-SY5Y cells treated with 5 $\mu$ M A $\beta$  and 500  $\mu$ M BSO for 46 hours were rescued to 91% by ferrostatin I. C11-Bodipy staining and 4-HNE analysis by both immunoblotting and staining showed increased lipid peroxidation in both the approaches. On the

other hand, Caspase-3 was not found to have been activated, nor the pan caspase inhibitors rescued the cells in any of the approaches. These findings suggest that A $\beta$  accumulation in combination with reduced intracellular GSH, may induce neuron-like cell death via lipid peroxidation-dependent mechanism, consistent with ferroptosis.

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## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.15/D11

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

**Support:** Cure Alzheimer's Fund

**Title:** Amyloid- $\beta$  Mediated inhibition of  $\gamma$ -secretase activity impairs endolysosomal network: implications in alzheimer's disease

**Authors:** \*U. DAS<sup>1</sup>, D. MILLER<sup>1</sup>, A. JOHNSTONE<sup>2</sup>, D. KARACHENTSEV<sup>1</sup>, X. ZUO<sup>3</sup>, X.-Q. CHEN<sup>4</sup>, A. BECKER<sup>1</sup>, W. C. MOBLEY<sup>5</sup>;

<sup>1</sup>Univ. of California San Diego, La Jolla, CA; <sup>2</sup>UCSD, San Diego, CA; <sup>3</sup>UCSD, SAN DIEGO, CA; <sup>4</sup>Neurosciences, UCSD/Neuroscience, La Jolla, CA; <sup>5</sup>Dept. of Neurosciences, Univ. of California San Diego Dept. of Neurosciences, La Jolla, CA

**Abstract:** In Alzheimer's disease and Down Syndrome, two highly prevalent but interlinked neurodegenerative disorders, amyloid beta (A $\beta$ ) peptides accumulate in the brain decades before dementia. A large body of evidence supports the hypothesis that longer A $\beta$  peptides ( $\geq 42$  aa) trigger pathogenic cascades that eventually lead to neurodegeneration. However, there is no consensus on how A $\beta$  acts. Herein, we propose a novel mechanism that connects pathological increases in A $\beta_{\geq 42}$  to dysregulation of multiple homeostatic pathways. We hypothesize that accumulation of A $\beta_{42}$  in endo-lysosomal (EL) compartments inhibits gamma-secretase ( $\gamma$ -secretase) activities, leading to increased levels of unprocessed substrates, including APP-CTFs, that dysregulate cell functions, including the EL network (ELN) and EL membrane injury.

**Methods:** We used recombinant human A $\beta_{42}$  and biologically derived A $\beta$  in cell-free and cellular systems to measure  $\gamma$ -secretase activity and accumulation of various  $\gamma$ -secretase substrates, including APP-CTFs. Subsequently, we investigated changes in the ELN pathways in neuronal and microglial cell lines using biochemical techniques and immunofluorescence microscopy. **Results:** We found that human A $\beta_{42}$  inhibited  $\gamma$ -secretase in cell-free conditions. In cellular systems, recombinant human A $\beta_{42}$  and biologically derived A $\beta$  increased the accumulation of APP-CTFs. Remarkably, neither murine A $\beta_{42}$  nor human A $\beta_{40}$  peptides inhibited the enzyme. Importantly, the accumulation of APP-CTFs resulted in the hyperactivation of RAB5 (GTP-Rab5), the small GTPase that regulates the fusion and trafficking of early endosomes, and the altered rate of receptor endocytosis. Further, the increased GTP-

Rab5 level recruited adaptor protein, APPL1, to EE membranes, and potentially triggered EE fusion to create enlarged EE. Our data also indicate EL membrane injury and changes in the levels of lysosomal enzymes and their activities. An increase in APP-CTF levels in AD synaptosomes points toward a similar mechanism of  $\gamma$ -secretase inhibition by A $\beta$  in Alzheimer's brains. **Conclusions:** Our findings discover a previously unknown function of A $\beta$  and indicate that A $\beta$ 42 contributes to AD and DSAD pathology through inhibition of  $\gamma$ -secretase activity. Our data support the hypothesis that accumulation of A $\beta$ 42 in the ELN compartments inhibits  $\gamma$ -secretase activities, leading to increased levels of unprocessed substrates that dysregulate cell function, including the EL network (ELN).

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## Poster

### PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.16/D12

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

**Support:** KGM4562532

**Title:** Longitudinal assessment of circadian and behavioral alterations in a non-human primate model of Alzheimer's disease

**Authors:** \*Y. KIM<sup>1,5</sup>, J. PARK<sup>2</sup>, J. WON<sup>6</sup>, K. LIM<sup>3</sup>, C.-Y. JEON<sup>7</sup>, G.-S. BAE<sup>4</sup>, E. JEON<sup>4</sup>, Y. LEE<sup>8</sup>;

<sup>1</sup>Korea Res. Inst. of Biosci. and Biotech., Cheongju-si, Korea, Republic of; <sup>2</sup>Natl. Primate Res. Ctr., Korea Res. Inst. of Biosci. and Biotech., Cheongju, Korea, Republic of; <sup>3</sup>Futuristic Animal Resource and Res. Ctr., Korea Res. Inst. of Biosci. and Biotech., Chungju, Korea, Republic of; <sup>4</sup>Natl. Primate Res. Ctr., Korea Res. Inst. of Biosci. and Biotech., Cheongju-si, Korea, Republic of; <sup>5</sup>Biosci., Univ. of Sci. and Technol. (UST), Daejeon, Korea, Republic of; <sup>6</sup>Natl. Primate Res. Ctr., Korea Res. Inst. of Biosci. & Biotech., Cheongju-si, Korea, Republic of; <sup>7</sup>Natl. Primate Res. Ctr., Korea Res. Inst. of Biosci. and Biotech., Cheonju-Si, Korea, Republic of; <sup>8</sup>Natl. Primate Res. Ctr., NPREC, KRIBB, Cheongju, Korea, Republic of

**Abstract:** This study aimed to examine activity-related and behavioral alterations associated with the early progression of Alzheimer's disease (AD) using a long-term non-human primate (NHP) model. The model was established through repeated cisterna magna (CM) administrations of amyloid beta 1-42 (A $\beta$ 1-42) oligomers. To monitor behavioral and cognitive changes, a touchscreen-based testing system was employed, enabling sensitive and longitudinal assessment of psychological and cognitive functions. Simultaneously, daily activity patterns were continuously tracked using an accelerometer embedded in a wearable necklace, allowing for the detection of circadian and behavioral fluctuations. Following A $\beta$ 1-42 oligomer injections,

marked disruptions in activity rhythms were observed. Both nocturnal and diurnal activity levels increased significantly, suggesting impairments in normal rest-activity cycles. Furthermore, the typical peak of activity was shifted indicating disturbances in circadian timing, which may reflect early disruptions of the sleep-wake cycle commonly observed in AD patients. These alterations were most pronounced approximately one month post-injection, followed by partial recovery over time. In addition to physiological changes, behavioral assessments revealed psychological alterations, including increased stubbornness and decreased motivation - symptoms that closely resemble affective features seen in the early stages of AD. Notably, despite these behavioral and circadian disruptions, cognitive performance remained stable throughout the nine-month observation period, with no significant decline detected. These findings demonstrate that the long-term NHP model effectively recapitulates early behavioral and circadian abnormalities associated with AD pathology, even in the absence of detectable cognitive impairment. This model thus represents a valuable tool for investigating the prodromal phase of AD. Future studies will incorporate neuroimaging techniques and analyses of blood and cerebrospinal fluid (CSF) biomarkers to further characterize disease progression and support the development of early diagnostic and therapeutic strategies.

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## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.17/D13

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

**Support:** Marie Skłodowska-Curie Actions (no. 101072895)

**Title:** Amyloid-beta and tau pathologies disrupt circadian clock homeostasis in Alzheimer's disease

**Authors:** \*X. HUANG<sup>1,2,3</sup>, D. ALBANI<sup>1</sup>;

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**Abstract: Introduction:** Circadian rhythm disruption represents both a risk factor and early manifestation of Alzheimer's disease (AD), characterized by sleep-wake cycle fragmentation and loss of circadian activity rhythmicity. While extracellular amyloid-beta (A $\beta$ ) plaques and intraneuronal neurofibrillary tau tangles are well-established pathological hallmarks of AD, the molecular mechanisms by which A $\beta$  and tau impair circadian clock regulation remain poorly understood. **Methods:** We established in vitro models using an H4 cell line stably expressing the APP695 Swedish double mutation (K595N/M596L) and a HEK293 cell line transfected with human tau P301L, alongside wild-type controls. Dexamethasone was employed as a zeitgeber to

synchronize cellular circadian rhythms. Based on post-mortem brain transcriptomic analyses from AD patients and healthy controls, we selected a panel of circadian clock-related genes and assessed their transcriptional profiles via RT-qPCR (TaqMan assays). Additionally, we assessed associated phenotypes, cellular functions, molecular pathways, and their correlation with circadian disruption in these models. **Results:** Both A $\beta$  and tau pathologies induced significant circadian gene dysregulation, marked by distinct patterns including phase shifts (acrophase alterations), phase inversion, and bidirectional amplitude modulation (both suppression and enhancement). Notably, A $\beta$  and tau exerted differential effects on circadian gene regulation. Core circadian clock proteins exhibited accelerated degradation and increased SUMOylation under AD pathological conditions. These disruptions were associated with downstream AD-related cascades, including mitochondrial dysfunction and elevated autophagy. **Conclusion:** Our findings suggest that A $\beta$  and tau pathologies disrupt molecular circadian homeostasis, potentially contributing to sleep disturbances in AD. Therapeutic strategies aimed at restoring circadian rhythms may offer a novel approach to slow AD progression and alleviate sleep-related symptoms.

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## Poster

### PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.18/D14

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

**Support:** NIA R01 AG068330 (PI: Macauley)  
BrightFocus Grant (PI: Macauley)  
CNS Metabolism COBRE P20 GM148326 (CoI: Macauley)  
CART grant (PI: Macauley)  
T32NS115704 (Constantino)

**Title:** Divergence of sleep phenotypes in Alzheimer's disease: NREM alterations emerge with amyloid-beta but increased REM vulnerability occurs with age

**Authors:** \*N. J. CONSTANTINO<sup>1,2</sup>, E. NEARY<sup>3</sup>, S. M. TURNER<sup>3</sup>, D. A. RUBINOW<sup>5</sup>, A. SNIPES<sup>3</sup>, S. L. MACAULEY<sup>3,4,2</sup>;

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**Abstract:** In Alzheimer's disease (AD), amyloid-beta (A $\beta$ ) pathology is linked to sleep disturbances. However, it is unclear whether sleep loss correlates with the total amount of A $\beta$  deposition and how aging impacts these phenotypes. To explore this relationship, we examined sleep in 3-, 6- and 18-month APP/PS1 and wildtype (WT) mice. At 6 months, less than 1% of the cortex had A $\beta$  deposition but there was a 22% reduction in NREM sleep. REM was sleep spared.

A $\beta$  deposition decreased slow wave sleep quality (delta) in NREM by 6 months. By 18 months, 20% of the cortex had A $\beta$  deposition, yet no further sleep loss occurred. This suggests that once A $\beta$  pathology develops, reductions in NREM sleep quantity and quality occur, but do not progress with more amyloid plaques. Interestingly, aging alone shifted the sleep phenotype by increasing NREM but decreasing REM sleep at 18 months. Power spectral analysis of EEG activity reveals poor REM sleep quality, with increased delta and decreased theta activity, due to age. This suggests abnormal REM sleep occurs with age. To further interrogate these sleep phenotypes, we used a sleep deprivation (SD) challenge to determine whether age and A $\beta$  deposition affect sleep rebound. In young WT mice, sleep rebound peaked three hours post-SD, where NREM and REM sleep increased by 60% and 67%, respectively, compared to baseline sleep. Furthermore, homeostatic sleep drive (delta) and NREM sleep quality (delta) increased during this period. At 6 months, both APP/PS1 and WT mice display comparable levels of sleep rebound compared to their baselines, suggesting A $\beta$  pathology does not affect sleep rebound during early stages of plaque formation. By 18 months, both APP/PS1 and WT mice lose sleep rebound compared to baseline, suggesting that age, not pathology, impacts rebound sleep. Compared to young mice, we found that aging eliminates REM sleep rebound, whereas A $\beta$  eliminates NREM sleep rebound. This study was the first of its kind to explore how A $\beta$  and aging interact to affect sleep macro- and micro-architecture. We found that once A $\beta$  plaques form, NREM sleep deficits emerge and plateau. This suggests that NREM sleep is an important biomarker for early A $\beta$  aggregation, potentially identifying individuals in midlife who are amyloid-positive. Interestingly, aging impacts sleep phenotypes differentially, by reducing REM sleep. Finally, A $\beta$  does not seem to impact sleep rebound during the early stages of plaque formation, but ultimately sleep rebound is lost with aging. Together, these studies highlight how sleep phenotypes change relative to A $\beta$  or aging, highlighting the vulnerability to sleep loss with age.

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## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.19/D15

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

**Support:** NIA5R01AG070934-03

**Title:** Impact of the gut-brain axis on amyloid beta pathogenesis in the brain of Alzheimer's disease mouse model

**Authors:** \*T. K. DAS<sup>1</sup>, J. M. MENDOZA<sup>1</sup>, B. P. GANESH<sup>1,2</sup>, M. BLASCO-CONESA<sup>1</sup>, G. ALROUSAN<sup>1</sup>;



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**Abstract:** Alzheimer's disease (AD) is the most prevalent form of dementia among older adults, yet its exact cause and origin remain unclear. Recent research suggests that pathogenic bacteria produce amyloid-like proteins known as bacterial amyloid, that form biofilms, which may impact the "gut-brain axis" and contribute to the progression of AD. Thus, we hypothesize that early gut inflammation may promote A $\beta$  pathology via activation of toll-like receptors (TLRs) in the brain. Tg2576 AD mice, which typically exhibit pathology at 11 to 12 months of age, were studied at 6 months (pre-symptomatic), 9 months (pre-symptomatic), and 15 months (symptomatic), along with age-matched wild-type littermate controls. Mild ulcerative colitis like gut inflammation was caused by administration of dextran sulfate sodium (DSS) prior to A $\beta$  pathology and disease progression in the brain was analyzed longitudinally. Behavioral studies were conducted at 6, 9, and 15 months of age. TLRs and A $\beta$  40/42 expression levels were analyzed. 16S rRNA gene sequencing was employed to assess bacterial gut dysbiosis and total RNA seq analysis was performed in brains. We utilized dorsal root ganglion (DRG) neurons in electrophysiological experiments to investigate the role of bacterial amyloid in gut-brain axis interaction. All data were compared between age-matched, water-treated mice. DSS-treated Tg(+) mice at pre-symptomatic timepoint of 9 months of age showed significant cognitive decline compared to littermate controls, as measured by the Y-Maze test. Recognition memory, assessed using the Novel Object Recognition Test, was also notably impaired in DSS-treated Tg(+) mice at 9 months. Microglial morphology was significantly altered in the brains of DSS-treated Tg(+) mice compared to those of water-treated Tg(+) mice at 9 months. TLR2 expression was significantly elevated in the brains of DSS-treated Tg(+) mice at 9 months compared to the water-treated mice. A notable increase in gram-positive bacterial colonization was observed in the ileum, along with heightened levels of bacterial amyloid. Our findings revealed that DRG neurons treated with bacterial amyloid in vivo exhibited pronounced electrophysiological responses, suggesting a direct or indirect effect on neuronal excitability. This suggests that early gut inflammation may contribute to the onset of A $\beta$  pathology in the brain, potentially through the activation of TLR-specific gut-brain axis signaling in Alzheimer's disease. Early detection approach offers insights into the initiation and progression of AD, paving the way for the development of novel preventive and therapeutic strategies.

**Disclosures:** T.K. Das: None. J.M. Mendoza: None. B.P. Ganesh: None. M. Blasco-Conesa: None. G. Alrousan: None.

## **Poster**

### **PSTR209: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR209.20/D16

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

**Support:** NIH Grant AG068215  
Lyman T Johnson Fellowship

**Title:** Chronic Sleep Fragmentation Reshapes Slow-wave Sleep Homeostasis in the APP/PS1 Knock-In Mouse

**Authors:** \*G. MORILLO SEGOVIA<sup>1</sup>, M. LAVIN<sup>2</sup>, D. IRADUKUNDA<sup>2</sup>, M. P. MURPHY<sup>3</sup>, A. D. BACHSTETTER<sup>4</sup>, M. J. DUNCAN<sup>4</sup>, B. F. O'HARA<sup>5</sup>, S. SUNDERAM<sup>2</sup>;  
<sup>2</sup>Dept. of Biomed. Engin., <sup>3</sup>Mol. and Cell. Biochem., <sup>4</sup>Dept. of Neurosci., <sup>5</sup>Dept. of Biol., <sup>1</sup>Univ. of Kentucky, Lexington, KY

**Abstract:** Sleep is critical for brain function and cognitive health, playing a key role in the clearance of amyloid  $\beta$  ( $A\beta$ ), a protein implicated in Alzheimer's disease (AD) pathology. However, sleep fragmentation (SF), characterized by repetitive interruptions of the sleep-wake cycle, is common in AD patients and may exacerbate pathological processes, including increased  $A\beta$  accumulation. While it is generally accepted that reduced slow wave sleep increases  $A\beta$  accumulation, the dynamics of slow wave activity (SWA) during chronic SF are poorly characterized. With institutional approval, we used electroencephalography (EEG) and electromyography (EMG) recordings to examine how chronic SF influences non-rapid eye movement (NREM) sleep and SWA in male APP/PS1 knock-in mice (8 or 11 months, N=8 per condition). After a baseline recording, animals underwent a four-week-long protocol with four daily 1-hour SF periods separated by 90-minute undisturbed intervals in the light phase. Sleep scores were obtained using machine learning applied to EEG/EMG features and verified manually. NREM/REM durations, mean bout lengths, and slow wave density (SWD), defined as relative 0.5-4 Hz EEG power per NREM epoch, were measured. After 4 weeks, animals were euthanized and cortical and hippocampal  $A\beta$  levels assessed via 6E10 immunohistochemistry. SF mice showed a significant reduction (~40%) in NREM duration and bout length during the periods of SF. Despite this, total daily NREM increased steadily over time, matching control levels by week 2 and then exceeding them. By week 4, NREM bouts during undisturbed intervals became significantly longer than baseline, indicating increased sleep drive and recovery. REM sleep showed some initial deficits but normalized over the treatment period. Lastly, SF led to significant increases in SWD during fragmented blocks, indicating increased slow wave efficiency during brief sleep bouts. However, despite compensatory adaptations in response to SF, cortical  $A\beta$  accumulation was significantly elevated in SF mice, while hippocampal  $A\beta$  seemed unaffected compared to controls. Our findings reveal that chronic SF induces adaptive changes in sleep structure and SWA dynamics but promotes  $A\beta$  deposition, highlighting the complexity of homeostatic sleep recovery under conditions of prolonged fragmentation.

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**Poster**

**PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.01/D17

**Topic:** C.03. Parkinson's Disease

**Title:** Altered Firing Dynamics of Narrow-Spiking Neurons in the Subthalamic nucleus of Parkinson's Patients

**Authors:** \*J. SINGH<sup>1</sup>, K. HOANG<sup>2</sup>, Y. B. BEZCHLIBNYK<sup>2</sup>, S. MOLOTCHNIKOFF<sup>3</sup>, O. FLOUTY<sup>2</sup>, V. BHARMAURIA<sup>2,4</sup>;

<sup>2</sup>The Tampa Human Neurophysiol. Lab. & Dept. of Neurosurgery, Brain and Spine, <sup>1</sup>Univ. of South Florida Morsani Col. of Med., Tampa, FL; <sup>3</sup>Sci. Biologiques, Univ. de Montreal, Montreal, QC, Canada; <sup>4</sup>Ctr. for Vision Res. & Ctr. for Integrative and Applied Neurosci., Toronto, ON, Canada

**Abstract:** Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor dysfunction, including tremor, bradykinesia, and rigidity, arising from disrupted neuronal connectivity within the basal ganglia (McGregor et al., 2019). Deep brain stimulation (DBS) effectively targets the subthalamic nucleus (STN) or globus pallidus internus to modulate aberrant neural activity and alleviate symptoms (Shaheen et al., 2024). During DBS implantation, microelectrode recordings (MER) are used intraoperatively to map neural activity and optimize lead placement. However, comprehensive characterization of neuronal firing patterns within tremor-associated regions remains limited. In this study, multiunit activity was recorded intraoperatively from the STN and surrounding regions using NeuroOmega during DBS surgery in 9 PD patients. Neurons were isolated using Spike2 and classified by spike-width into Broad-Spiking (BS), Narrow-Spiking (NS), and Triphasic (TPh) types. Tremor-zone neurons were identified intraoperatively by the neurosurgeon. We analyzed 86 Tremor-zone (44 BS, 28 NS, 14 TPh) and 197 Non-Tremor-zone neurons (90 BS, 61 NS, 46 TPh). No significant difference was noticed in the distribution of neuron types between Tremor and Non-Tremor groups ( $\chi^2(2) = 1.84$ ,  $p = 0.40$ ). Firing properties were quantified using coefficient of variation (CV), local variation (LV), burst index (BI), and log-normal fits on inter-spike interval (log ISI). Among NS neurons, CV was significantly lower in tremor compared with non-tremor neurons ( $p = 0.025$ ), suggesting increased firing regularity and possible enhancement of burst-like behavior within Tremor-associated circuits. LV also showed a trend toward significance in NS neurons ( $p = 0.057$ ) further pointing toward altered firing regularity, network integration, or inhibitory dynamics. Comparison of log ISI fits revealed no significant overall difference between Tremor and Non-Tremor neurons ( $p = 0.28$ ), although TPh log ISIs nearly reached significance ( $p = 0.061$ ), warranting further investigation. No significant differences were observed in BS or TPh neurons across CV, LV, BI, or log ISI. Our results indicate that tremor-related activity in PD is not driven by differences in neuronal subtype distribution but by altered functional dynamics. Specifically, NS neurons in Tremor zones exhibit increased firing regularity, suggesting disrupted inhibitory control. This points to a circuit-level imbalance in excitatory-inhibitory interactions as a key contributor to tremor generation.

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## Poster

### PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.02/D18

**Topic:** C.03. Parkinson's Disease

**Support:** UG3-NS130202  
UH3-NS130202  
1K23NS117735

**Title:** Cognitive control mechanisms in patients with movement disorders undergoing deep brain stimulation surgery

**Authors:** \*A. MYSORE<sup>1</sup>, M. T. HOLLAND<sup>2</sup>, J. THUM<sup>3</sup>, H. C. WALKER<sup>4</sup>, N. BENTLEY<sup>2</sup>; <sup>2</sup>Neurosurg., <sup>1</sup>Univ. of Alabama at Birmingham, Birmingham, AL; <sup>3</sup>Univ. of Alabama, Birmingham, Birmingham, AL; <sup>4</sup>Neurol., UAB Neurosciences Programs, Birmingham, AL

**Abstract: Introduction:** Cognitive control depends on critically processing incoming sensory information from the environment and using relevant cues to precisely govern actions. Motor control can occur in an anticipatory (proactive) or late-corrective (reactive) manner. Parkinson's disease patients often struggle with cognitive control and their scalp potentials during these behaviors differ from healthy controls. However, the spatiotemporal dynamics of these EEG signals is highly debated. Here we sought to better understand the neural basis of cognitive control in patients with movement disorders using temporary subdural recordings from cerebral cortex during deep brain stimulation (DBS) surgery. **Methods:** Five patients (four with Parkinson's disease and one with essential tremor) performed an AX-version of the continuous performance task (AX-CPT) during DBS surgery. This task evaluates behavioral deficits of cognitive control by requiring the patient to respond to a probe stimulus based on preceding contextual cue conditioning. In AX-CPT, the probabilistic context allows multiple action choices which requires reactive control after delivery of the probe. In contrast, the deterministic context has a cue-conditioned single action choice which requires proactive control. To observe neural interactions between brain areas associated with cognitive control, two six-contact electrocorticography (ECoG) strips were temporarily placed along the cortex during routine clinical DBS surgery: one anteriorly over prefrontal cortex and one posteriorly over primary motor cortex, ipsilateral to the DBS implant. After completion of the task, the strips were removed. **Results:** Two patients with Parkinson's disease had higher error rates and slower response times in the deterministic context. The others displayed lower error rates and faster response times in the deterministic context. Additionally, anterior ECoG contacts in the left hemisphere displayed context-based amplitude differences in the anticipatory response interval between the contextual cue and probe stimulus. Ongoing analyses are evaluating the spatiotemporal dynamics of these responses from dorsolateral prefrontal cortex, primary motor cortex, and basal ganglia recording sites. **Conclusion:** In this pilot study, half of the participants had difficulty engaging proactive control, with an increased reliance on reactive control. This

finding represents a different pattern of cognitive control compared to healthy individuals and warrants further investigation. Future studies will examine the spatiotemporal dynamics of these responses by recording site, brain hemisphere, and disease.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.03/D19

**Topic:** C.03. Parkinson's Disease

**Support:** NIH NINDS Grant UG3/UH3 NS130202

**Title:** Subthalamic nucleus deep brain stimulation local evoked potentials differ based on stimulation and recording depth in two patients with Parkinson disease

**Authors:** \*S. A. BRINKERHOFF<sup>1</sup>, A. NAKHMANI<sup>2</sup>, A. MYSORE<sup>3,1</sup>, M. T. HOLLAND<sup>3</sup>, N. BENTLEY<sup>3,2</sup>, J. THUM<sup>4</sup>, H. C. WALKER<sup>1,3,2</sup>;  
<sup>1</sup>Neurol., <sup>2</sup>Electrical & Computer Engin., <sup>3</sup>Neurosurg., Univ. of Alabama at Birmingham, Birmingham, AL; <sup>4</sup>Univ. of Alabama, Birmingham.

**Abstract:** Introduction: Deep brain stimulation (DBS) is an established treatment for Parkinson disease. Subthalamic nucleus DBS evokes multiple local neural responses, including an oscillatory response — evoked resonant neural activity (ERNA). DBS contacts that record larger ERNA amplitudes often correlate with DBS contacts selected for therapy, suggesting ERNA may spatially originate near an ideal stimulation site in the subthalamic nucleus. While ERNA appears to change with recording location, it is unclear how ERNA may also change with stimulation location. Mapping its spatial origin may reveal its utility for therapeutic current steering in subthalamic nucleus DBS. Methods: 2 patients with PD underwent awake unilateral subthalamic nucleus DBS surgery (8-contact directional lead). During implant, we advanced the lead at 2 mm intervals from the target (n=6 depths) and delivered monopolar stimulation from one ventral directional contact, recording from the remaining 7 contacts. We delivered identical stimulation at each depth: 15 single 3mA biphasic pulses with 60μsec phase widths. We constructed bipolar montages between horizontal adjacent directional contacts, applied continuous wavelet transforms to the referenced signals, and normalized to peak power with participant. We compared ERNA frequency and power as a function of stimulation and recording sites along the dorsoventral axis of the DBS trajectory. The stimulation contact remained constant, so that around-the-lead stimulation location remained fixed. Results : Results were similar in both patients. ERNA was absent when stimulation was in white matter dorsal to the subthalamic nucleus but appeared when stimulation reached its dorsal border. ERNA frequency increased from 250 to 350 Hz as stimulation depth increased. Patient-normalized ERNA power

also increased with stimulation depth and was maximal when stimulation occurred at the ventral subthalamic nucleus border and the neural response recorded within the central-dorsal subthalamic nucleus. Conclusions: In 2 patients with PD, an ERNA response to a single DBS pulse was observed only when stimulation entered the subthalamic nucleus, suggesting that ERNA originates from neural activity within the subthalamic nucleus, specifically from tissue near the dorsoventral center of the subthalamic nucleus. Larger sample sizes and additional mapping of around-the-lead stimulation changes are needed to localize the origin of ERNA. These findings support the potential of ERNA as a marker for identifying functionally relevant subthalamic nucleus subregions, which may improve therapeutic targeting and current steering during DBS programming.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.04/D20

**Topic:** C.03. Parkinson's Disease

**Support:** UG3NS130202  
UH3NS100553

**Title:** Modulation of cross- and intra-structure phase-amplitude coupling in motor cortex and basal ganglia in patients with Parkinson's disease

**Authors:** \*J. JADAPALLI<sup>1</sup>, M. NOOR<sup>2</sup>, Z. T. IRWIN<sup>3</sup>, J. OLSON<sup>5</sup>, A. NAKHMANI<sup>6</sup>, C. GONZALEZ<sup>4</sup>, H. C. WALKER<sup>7</sup>;

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**Abstract:** Spatially distributed neural networks contribute to both motor control and the pathophysiology of Parkinson's disease, yet the functional interactions between nodes within these circuits remain poorly understood. Deep brain stimulation (DBS), while effective in treating motor symptoms, also provides a unique opportunity to probe these network dynamics. In this study, we analyzed local field potentials (LFPs) from the hand area of motor cortex and the subthalamic nucleus (STN) in 25 patients with Parkinson's disease undergoing DBS surgery. Data was recorded at 25 kHz during rest and both active and passive contralateral upper limb movements. Cortical LFPs were referenced using an adjacent bipolar montage, while LFPs from directional DBS contacts were referenced in a vertical bipolar scheme to optimize the signal-to-

noise ratio - resulting in 27.4% and 24.3% increases in beta power compared to horizontal and common average references, respectively. We then calculated phase-amplitude coupling both within and between these brain regions.

Within individual structures, the strongest coupling was observed at rest. In primary motor cortex, coupling was most prominent between alpha and low beta frequency (8-20 Hz) phase and high-frequency (65-150 Hz) amplitude, whereas in primary sensory cortex, coupling occurred between a broader low frequency (2-30 Hz) phase and high frequency (65-250 Hz) amplitude. In the STN, however, beta band (13-30 Hz) phase coupled most strongly to amplitudes at even higher frequencies (200-600 Hz). Both active and passive movements suppressed phase amplitude coupling, albeit more strongly in cerebral cortex than in the STN.

Across regions, we observed robust coupling at rest between beta-phase activity in primary motor and sensory cortices and high-frequency (100-300 Hz) amplitude in the STN. In contrast, movements - both passive and active - shifted inter-regional coupling to low-frequency phase (2-12 Hz; delta, theta, alpha) in the STN and high-frequency (65-100 Hz) amplitude in cortical regions.

These findings reveal task-dependent, bi-directional modulation of phase amplitude coupling within and across motor-related brain regions. Our results suggest that distinct frequency bands serve as dynamic communication channels between cortex and STN, and that bottom-up sensorimotor integration from STN may modulate cortical excitability during motor task execution. Future studies should examine how this physiology relates to both normal motor processing and network-level dysfunction in Parkinson's disease.

**Disclosures:** J. Jadapalli: None. M. Noor: None. Z.T. Irwin: None. J. Olson: None. A. Nakhmani: None. C. Gonzalez: None. H.C. Walker: None.

## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.05/D21

**Topic:** C.03. Parkinson's Disease

**Support:** NIH NINDS P50NS123109  
NIH NINDS R01NS131371  
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NIH NINDS 5T32NS121920-03  
MnDRIVE Brain Conditions Program  
Engdahl Family Foundation

**Title:** Sleep stage decoding in Parkinson's disease using pallidal oscillatory activity

**Authors:** \*J. FROULA<sup>1</sup>, J. BUENO DIAZ<sup>2</sup>, A. VERMA<sup>1</sup>, J. E. AMAN<sup>1</sup>, J. WANG<sup>1</sup>, A. PEARSON<sup>5</sup>, M. HILL<sup>2</sup>, R. PATRIAT<sup>2</sup>, S. E. COOPER<sup>1</sup>, N. HAREL<sup>6</sup>, M. C. PARK<sup>3</sup>, M. HOWELL<sup>2</sup>, C. D. MACKINNON<sup>1</sup>, J. L. VITEK, MD, PHD<sup>4</sup>, L. A. JOHNSON<sup>7</sup>;

<sup>1</sup>Neurol., <sup>3</sup>Neurosurg., <sup>4</sup>Dept. of Neurol., <sup>2</sup>Univ. of Minnesota, Minneapolis, MN; <sup>6</sup>Radiology, <sup>5</sup>Univ. of Minnesota Syst., Minneapolis, MN; <sup>7</sup>Univ. of Minnesota Dept of Neurol., Univ. of Minnesota, Twin Cities, Minneapolis, MN

**Abstract:** Sleep disturbances adversely impact a majority of people with Parkinson's disease (PD), yet impactful treatments are lacking. While deep brain stimulation (DBS) of the globus pallidus internus (GPi) is effective for treatment of motor signs in PD, the potential utility of GPi DBS for treating disordered sleep is unclear. Adaptive, sleep stage-specific DBS is a promising approach to improve sleep but will likely require online decoding of sleep stages based on recordings from the DBS lead. It is not well understood, however, how spectral characteristics of GPi oscillatory activity are modulated during non-REM (NREM) and REM sleep compared to the wake state. In this study, we characterized GPi neurophysiology across directional lead segments (directions defined as A, B, and C) during wake and NREM and REM sleep and examined their utility for sleep stage classification.

Video-polysomnography was simultaneously recorded with GPi oscillatory activity in four subjects (2M/2F) with externalized GPi leads (1-3-3-1 configuration). Wake, NREM stages 1-3, and REM were scored over 30-second intervals. Median spectral power was calculated over 10-s intervals and compared between stages in the following frequency bands: delta, 0.5-4 Hz; theta, 4-8 Hz; alpha, 8-13 Hz; beta, 13-35 Hz; low gamma, 35-90 Hz; high gamma, 90-150 Hz; and high-frequency (HFOs), 150-350 Hz. Features of band power across stages were used to train a weighted k-nearest neighbor algorithm to classify wake, NREM, and REM. We noted high variability of delta, theta, and alpha band power; no specific feature in these bands consistently indicated a specific stage. By contrast, beta, gamma, and HFO power for every directional segment (e.g., 2A-3A) was lowest in NREM across all subjects. Distinctions between wake and REM were also found in all subjects in at least one frequency band between 13-350 Hz. Accordingly, features between 13-350 Hz were most useful for classification, with the top feature in each subject yielding 70-80% accuracy when considered alone. Use of all spectral features achieved the following sleep classification accuracy for each directional segment: A:  $86.1 \pm 2.5\%$ ; B:  $87.8 \pm 6.0\%$ ; C:  $86.6 \pm 1.9\%$ . Top features and classification accuracy varied across segments and subjects, suggesting spectral activity between segments can impact accuracy.

These findings offer an improved understanding of GPi oscillatory dynamics in people with PD across the sleep-wake cycle. They also indicate GPi activity, particularly in beta, gamma and HFO frequencies, can be utilized for accurate sleep stage decoding within individuals. This information can help inform future development of adaptive DBS for sleep in PD.

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Inc., NeuroOne, Boston Scientific. Other; Listed faculty for University of Minnesota Educational Partnership with Medtronic, Inc., Minneapolis, MN. **M. Howell:** None. **C.D. MacKinnon:** None. **J.L. Vitek, MD, PhD:** 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.; Abbott, National Institutes of Health. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences, Inc.. F. Consulting Fees (e.g., advisory boards); Medtronic, Inc., Boston Scientific, Abbott, Surgical Information Sciences, Inc.. **L.A. Johnson:** None.

## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.06/D22

**Topic:** C.03. Parkinson's Disease

**Support:** University of South Florida

**Title:** Depth-resolved Characterization of Neuronal types in the Human Subthalamic Nucleus during Parkinson's Disease Surgery

**Authors:** \***K. HOANG**<sup>1</sup>, **J. SINGH**<sup>1</sup>, **Y. B. BEZCHLIBNYK**<sup>1</sup>, **S. MOLOTCHNIKOFF**<sup>2</sup>, **V. BHARMAURIA**<sup>1</sup>, **O. FLOUTY**<sup>1</sup>;

<sup>1</sup>Univ. of South Florida, Tampa, FL; <sup>2</sup>Sci. Biologiques, Univ. de Montreal, Montreal, QC, Canada

**Abstract:** Parkinson's disease (PD), the second most common neurodegenerative disorder in the U.S., is characterized by dopaminergic neuron loss in the substantia nigra pars compacta (SNc), leading to motor symptoms such as tremor, bradykinesia, and rigidity (Shaheen et al 2024). This neuronal loss disrupts basal ganglia circuitry by overactivating the indirect pathway and underactivating the direct pathway. The subthalamic nucleus (STN), a key node in this circuit, exhibits abnormal activity in PD. Imbalances in excitatory / inhibitory circuits between different neuronal types may lead to disrupted glutamatergic input to GPi/SNr, thus affecting thalamic regulation. While exact neural mechanisms remain unclear, investigating neuronal connectivity in the STN can deepen our understanding of PD pathology. Deep brain stimulation (DBS), a widely used PD treatment, modulates these dysfunctional circuits. During DBS surgery, microelectrodes are lowered in the STN and surrounding areas to map the neuronal activity across different depths (depth = 0 being the target). Here, we isolated neurons (Spike2, CED Cambridge) and then classified them based on spike-width (trough-to-peak cut-off threshold of 250  $\mu$ s): 449 broad-spiking (BS, presumed excitatory), 254 narrow-spiking (NS, putative inhibitory), and 230 triphasic neurons (TPh, putative axonal output) (Seo et al. 2024). We then quantified the neural activity across these classes by fitting log-normal fits [peak log(ISI)]. Significant differences in peak log(ISI) emerged among these groups (Kruskal-Wallis,  $p =$

0.0040), including BS vs. TPh ( $p = 0.0153$ ) and NS vs. TPh ( $p = 0.0057$ ). Depth-specific analysis revealed significant differences in firing patterns in the STN motor area (approx. 4-6 mm above target): BS vs. TPh at 4-4.999 mm ( $p = 0.0415$ ); BS vs. NS at 5-5.999 mm ( $p = 0.0264$ ) exhibited markedly different bursting rates for neurons, suggesting a different equilibrium between excitatory and inhibitory activity within the STN than other depths. In addition, significant differences in local variation (LV) at 5-5.999 mm (Kruskal-Wallis,  $p = 0.022$ ) and coefficient of variation (CV) at 6-6.999 mm (Kruskal-Wallis,  $p = 0.021$ ) were observed among the three neuron types. TPh showed lower bursting than both BS and NS, highlighting its uncertain but potentially distinct role in PD. Future analysis will employ machine learning algorithms to better understand neuronal types and their roles.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.07/D23

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant R01NS117822  
NIH Grant UH3NS125162  
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Engdhal Family Foundation  
MnDRIVE Brain Conditions Program

**Title:** Frequency-dependent effects of coordinated reset deep brain stimulation on parkinsonian motor signs in the non-human primate model of Parkinson's disease

**Authors:** \*K. NAKAJIMA, L. ZHENG, J. WANG, S. AMOOZEGAR, L. A. JOHNSON, J. L. VITEK, MD, PHD;  
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**Abstract:** Parkinson's Disease (PD) is a neurodegenerative disorder that affects over 10 million people globally. While Deep Brain Stimulation (DBS) is an effective treatment for PD, its effect can be compromised by current spread-related side effects and motor benefits decay rapidly after stimulation cessation. Coordinated Reset (CR) DBS is a novel DBS approach designed to desynchronize abnormally synchronized neuronal populations using lower levels of burst stimulation across multiple contacts of the DBS lead. Previous studies in the nonhuman primate (NHP) model of PD have demonstrated the therapeutic effect of CR DBS on parkinsonian motor signs that can sustain hours or days after stimulation cessation, i.e., carryover effect. The impact

of varying the CR frequency (cycle rate), however, has not been systematically investigated in vivo, although modeling studies suggested that it can significantly affect the neuronal desynchronizing effect underlying the carryover benefits. This study investigated the carryover effect of subthalamic CR DBS using different cycle rates on parkinsonian motor signs in the NHP model of PD. Two animals were rendered parkinsonian through injections of neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and each implanted with a DBS lead in the subthalamic nucleus (STN). Four cycle rates (5,7,8 and 9Hz) were evaluated in NHP B1 and five (5,6,7,8 and 9Hz) in NHP Bu. For each evaluation session, STN CR DBS was delivered for 2 hours/day for 5 consecutive days. A modified clinical rating scale (mUPDRS) and a quantitative gait assessment were performed before and after 5 days of CR treatment. Gait was assessed in a gait testing apparatus equipped with a gait mat system. In both animals, the 9 Hz cycle rate led to the greatest carryover improvement in the total mUPDRS score. Specifically, 9Hz cycle rate was associated with greatest carryover improvements in akinesia, rigidity and bradykinesia subscores in NHP B1 while mixed results were observed in NHP Bu. Cycle rates of 7 and 6 Hz produced the greatest carryover improvement in gait (increased stride length and swing speed) in NHP B1 and Bu, respectively. Although preliminary, this study demonstrates the importance of the selection of CR DBS parameters, especially the cycle rate, for different PD symptoms. Further research in more subjects is needed to validate our findings and to investigate the relationship between cycle rates and individual motor sign-related neural biomarkers. This study will further advance the development of CR DBS as an alternative treatment for PD that can potentially be customized based on each patient's phenotype.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.08/D24

**Topic:** C.03. Parkinson's Disease

**Support:** University of South Florida

**Title:** Comparative Efficacy of Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation in Parkinson's Disease: Synergistic Effects with Dopaminergic Medication

**Authors:** \*E. BLAZE<sup>1</sup>, N. SHAHEEN<sup>2</sup>, Y. B. BEZCHLIBNYK<sup>1</sup>, V. BHARMAURIA<sup>1</sup>, O. FLOUTY<sup>1</sup>;

<sup>1</sup>Univ. of South Florida, Tampa, FL; <sup>2</sup>Alexandria Univ., Alexandria, Egypt

**Abstract:** Deep brain stimulation (DBS) targeting the subthalamic nucleus (STN) or globus pallidus internus (GPi) is an established intervention for Parkinson's disease (PD) symptoms.

Although STN-DBS has historically been preferred for its potent motor benefits, emerging evidence and clinical experience underscore nuanced differences in efficacy and tolerability between the two targets. This study compares motor outcomes in PD patients undergoing STN-DBS or GPi-DBS, focusing on changes in Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor scores under various treatment conditions. Amongst 73 patients that were retrospectively analyzed, pre-operative UPDRS Part III off medication scores (mean  $\pm$  SEM,  $42.0 \pm 12.2$ ), improved to  $18.1 \pm 10.1$  on medication. Postoperatively, "on-stimulation/on-medication" scores were significantly lower in the STN-DBS group ( $11.3 \pm 9.2$ ), compared to the corresponding GPi-DBS group ( $15.2 \pm 9.9$ , Mann Whitney U Test,  $p=0.039$ ). Similarly, in the "on-stimulation/off-medication" state, STN-DBS scores ( $17.7 \pm 12.0$ ) were significantly lower than GPi-DBS ( $22.8 \pm 12.1$ ;  $p=0.038$ ) scores. Our results demonstrate a synergistic effect of STN-DBS with dopaminergic medication, yielding superior improvements in UPDRS Part III motor scores compared to GPi-DBS. However, STN-DBS carries a higher risk of side effects such as speech disturbances, cognitive decline, and mood changes, complicating postoperative care. In contrast, GPi-DBS provides more moderate but consistent motor benefits with fewer side effects, making it preferable for older or cognitively at-risk patients. Variability in medication types and dosages currently limits the generalizability of these outcomes. To address this, future analyses will normalize medication dosages to enable direct comparisons across patients. Ultimately, target selection should be individualized, balancing motor benefit, side effect risk, and patient preferences to optimize therapeutic outcomes.

**Disclosures:** E. Blaze: None. N. Shaheen: None. Y.B. Bezchlibnyk: None. V. Bharmauria: None. O. Flouty: None.

## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.09/D25

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant R37NS077657  
NIH Grant 5P50NS098573

**Title:** Differential Effects of Subthalamic Nucleus Deep Brain Stimulation and Levodopa on Task-Related Spiking in Dorsolateral Prefrontal Cortex

**Authors:** \*J. NOCON, B. MOHANTY, N. HJELLE, J. WANG, L. A. JOHNSON, J. L. VITEK, MD, PHD;  
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**Abstract:** The dorsolateral prefrontal cortex (DLPFC) is implicated in executive function, motor planning, and motivated action. Such cognitive functions can be impaired in Parkinson's disease (PD) and may be associated with abnormal DLPFC activity. While a recent study found reduced

task-related neuronal modulation in DLPFC along with impaired behavioral task performance in a mild parkinsonian state, there are no studies describing the changes in DLPFC neuronal activity in more advanced parkinsonian states or during therapeutic interventions that improve motor signs. The goal of this study was to report the change in task-related modulation of DLPFC neuronal activity in moderate parkinsonism and during therapeutic interventions with subthalamic nucleus deep brain stimulation (STN DBS) and administration of levodopa. A non-human primate (N=1) was trained on a food retrieval task and rendered moderately parkinsonian through the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Neuronal activity (n=153 units naïve; n=179 units post-MPTP) and kinematic data of the working arm were recorded in the parkinsonian state and during STN DBS, levodopa, and STN DBS+levodopa. We hypothesized that DLPFC would exhibit fewer task-modulated units in moderate parkinsonism, that each therapy would increase task-related activity, and DBS+levodopa would lead to the greatest increase in modulated neuronal activity. Following MPTP administration, the animal reached a moderate state of parkinsonism. Median reach and retrieval time increased from 1.3s in the naïve state to 3.2s in the parkinsonian state while the proportion of task-modulated units decreased from 82% to 36% ( $p=1e-10$ ). All treatments improved mUPDRS scores (DBS: 5.87, levodopa: 3.07, combined: 0.33) and reach and retrieval times improved (DBS: 2.2s, levodopa: 2.0s, combined: 1.7s). Levodopa increased the proportion of task-modulated units to 62% ( $p=1e-06$ ), DBS to 46% ( $p=0.053$ ), and DBS+levodopa to 49% ( $p=0.014$ ). Our results suggest that STN DBS may compromise the beneficial effects of levodopa on task-related neuronal modulation in the DLPFC and are consistent with previous reports of deficits in semantic verbal fluency and reduced blood volumes in DLPFC during STN DBS. These findings also illustrate the differential effect these therapies may have on motor versus other functions associated with DLPFC and further emphasizes the importance of understanding these interactions if we are to advance neuromodulation therapies for the treatment of PD.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.10/D26

**Topic:** C.03. Parkinson's Disease

**Support:** University of South Florida

**Title:** Neural population synchrony correlates with beta power in the subthalamic nucleus of Parkinson's patients: a mechanistic link

**Authors:** \*N. SHAHEEN<sup>1</sup>, Y. B. BEZCHLIBNYK<sup>2</sup>, S. MOLOTCHNIKOFF<sup>3</sup>, O. FLOUTY<sup>2</sup>, V. BHARMAURIA<sup>2</sup>;

<sup>1</sup>Alexandria Univ., Alexandria, Egypt; <sup>2</sup>Univ. of South Florida, Tampa, FL; <sup>3</sup>Univ. de Montreal, Montreal, QC, Canada

**Abstract:** Abnormal beta oscillatory activity within the subthalamic nucleus (STN) is a hallmark of Parkinson's disease (PD) pathophysiology, contributing to motor symptoms such as rigidity and bradykinesia (Shaheen et al 2024). These beta oscillations (typically in the 12-30 Hz range) have been proposed to reflect excessive neural synchrony, yet the precise relationship between beta power and local neuronal synchrony remains unclear. We hypothesized that increased synchrony between neuronal populations manifests as increased beta power, reflecting temporally precise local interactions, indicating common input from a brain area. To test this, we examined the relationship between neuronal synchrony and beta-band oscillations in the STN of PD patients by quantifying the probability of synchronous activity (PP) from the central peak of cross-correlograms (CCGs) computed between multiunit activity (defined as threshold crossings 2.5 standard deviations above the mean signal). Using multichannel (5-channel) electrophysiological recordings from the STN, we calculated CCGs across all channel pairs and extracted the PP as a synchrony index. Corresponding mean beta power values were derived from peri-event spectrograms (-50 to 50 ms in relation to the trigger event) for the same channel pairs. Across beta frequency sub-bands (12-30 Hz, 12-20 Hz, and 20-30 Hz), we observed a consistent and significant positive correlation between PP and beta power ( $r \approx 0.18-0.19$ ,  $p < 0.01$ ). This relationship supports the notion that local synchronous firing contributes to enhanced beta oscillatory activity in the STN. However, the modest correlation coefficients suggest that linear regression does not account for all variability, and other physiological, anatomical, or state-dependent factors may also contribute to beta power modulation in PD. This local synchrony may also be shaped by pathological input from upstream structures such as the cortex and globus pallidus, consistent with broader alterations in basal ganglia-thalamo-cortical circuitry seen in PD (Fischer et al 2019). Overall, these findings underscore a mechanistic link between increased neuronal synchrony and elevated beta-band activity and point toward local synchrony as a potential target for therapeutic modulation of pathological beta rhythms in Parkinson's disease.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.11/D27

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant R01NS117822  
NIH Grant R01NS037019  
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NIH Grant P50 NS123109

Engdahl Family Foundation  
MnDRIVE Brain Conditions Program

**Title:** Therapeutic subthalamic deep brain stimulation alters motor cortical neuronal responses to passive movements in parkinsonism

**Authors:** \*L. ZHENG<sup>1</sup>, S. AMOOZEGAR<sup>1</sup>, M. FIECAS<sup>2</sup>, L. A. JOHNSON<sup>1</sup>, J. L. VITEK, MD, PHD<sup>1</sup>, J. WANG<sup>1</sup>;

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**Abstract:** Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor impairments such as rigidity. Pathophysiology of rigidity has been associated with broadened somatosensory receptive fields in subcortical and cortical regions including the primary motor cortex (M1). Deep brain stimulation (DBS) is a well-established therapy for PD and can efficiently alleviate motor symptoms. How therapeutic DBS alters somatosensory processing in M1, however, has never been investigated. We hypothesize that therapeutic DBS can narrow the receptive field in M1. To test the hypothesis, we investigated the alteration in M1 neuronal activities during passive movements in a non-human primate (NHP) model of PD. A 96-channel Utah array was placed over the arm area of M1 and an 8-contact DBS lead implanted in the subthalamic nucleus (STN). The NHP was acclimated to passive limb manipulation. Therapeutic STN DBS was delivered for 4 hours daily across five days. Neuronal activities in M1 were recorded during passive upper limb manipulations (elbow and shoulder flexion/extension at ~0.5 Hz) performed before, multiple times during and after DBS. Movements of the NHP's wrist were captured using a motion capture system and synchronized with neural recordings. M1 single unit activities were detected and sorted in Offline Sorter. Correlation analysis between individual neuronal firing rates and wrist position and velocity during passive movements were conducted to assess M1 neuronal responses. Results showed that the proportion of M1 neurons correlated with wrist position and velocity decreased significantly from 100 minutes after DBS onset, while the strength of neuronal responses (degree of change in firing rate during passive movements) increased significantly starting from 40 minutes ON DBS. The number of kinematic parameters (i.e., wrist position and velocity during elbow and shoulder movements) associated with individual neuronal activity significantly decreased beginning at 100 minutes during DBS. Although preliminary, our results suggest that therapeutic STN DBS improves both the specificity and strength of neuronal responses to passive movement, leading to narrowed receptive fields in M1. Given that parkinsonian rigidity has been associated with excessive cortical neuronal responses that widens receptive field, our findings indicate that STN DBS might improve rigidity by reducing these excessive responses and restoring receptive field properties to those closer to the healthy condition. **Key words:** Parkinson's disease, deep brain stimulation, subthalamic nucleus, primary motor cortex, passive movement, single unit activity, receptive field

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**Poster**

## **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.12/D28

**Topic:** J.04. Physiological Methods

**Support:** NIH Grant: UH3NS125162

**Title:** Pilot Case Study on Thalamic Coordinated Reset Deep Brain Stimulation for Essential Tremor

**Authors:** \*S. MEKA<sup>1</sup>, P. M. GRUND<sup>7</sup>, S. AMOOZEGAR<sup>1</sup>, L. BRITO DE ALMEIDA<sup>2</sup>, J. E. AMAN<sup>3</sup>, S. ALBERICO<sup>3</sup>, M. D. JOHNSON<sup>4</sup>, N. HAREL<sup>9</sup>, S. E. COOPER<sup>3</sup>, M. C. PARK<sup>5</sup>, L. ZHENG<sup>6</sup>, L. A. JOHNSON<sup>8</sup>, J. L. VITEK, MD, PHD<sup>2</sup>, J. WANG<sup>3</sup>;

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**Abstract:** Despite the therapeutic advantages of traditional deep brain stimulation (T-DBS) for Essential Tremor (ET), patients often experience residual symptoms or adverse effects and some experience loss of benefits overtime, highlighting the need for novel DBS approaches. Coordinated Reset DBS (CR-DBS) delivers low-intensity burst stimulation through multiple contacts of the DBS lead, and was designed to counteract pathological neural synchrony with desynchronizing effect sustaining after stimulation cessation (carryover effect). As ET has been associated with tremor related oscillatory activity in the thalamus, we hypothesize that thalamic CR-DBS can treat ET. The objective of this study is to compare the acute and carryover effects of thalamic CR-DBS to clinically optimized T-DBS, evaluating the safety and efficacy of CR-DBS for ET. Two ET patients were implanted with the Boston Scientific Vercise Genus DBS system. Thalamic local field potentials (LFPs) were recorded intraoperatively, and inertial measurement unit sensors were placed on the patient's hand to monitor tremor wirelessly. Spectral analysis of LFPs was performed to characterize the frequency and power of tremor related oscillatory activity that was used to determine the CR-DBS stimulation parameters (frequency and stimulation contacts). Each subject received a week of CR-DBS and a week of T-DBS, with the order of DBS settings pseudo-randomized for each patient. Carryover OFF-DBS effect was measured, following a week of stimulation. Tremor Research Group Essential Tremor Assessment Scale (TETRAS) and a spiral task together with monitoring of the hand movement were used to assess the immediate (hours) effect of DBS on tremor. An at home spiral task and a wrist watch were used to monitor the long-term (days) acute and carryover effects. In both subjects, CR-DBS produced immediate tremor suppression, reflected in the reduced TETRAS score and less tremor during the spiral task. The immediate effect of CR-DBS was comparable to that achieved by T-DBS in one subject and slightly worse than T-DBS in the other. Long-term tremor suppression was, however, only observed in one subject, reflected by reduced proportion of time with tremor measured by the watch. No significant carryover effect was observed after either CR-DBS or T-DBS. Although data are limited, our case study suggests that CR-DBS is a



promising approach for tremor management and warrants further investigation in larger patient cohorts. This study also demonstrates the importance and feasibility of using quantitative assessment methods that facilitate objective measurement of tremor both at study visits and during the patient's daily life.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.13/D29

**Topic:** C.03. Parkinson's Disease

**Support:** R01NS037019  
R37NS077657  
R01NS110613  
R01NS058945

**Title:** A modular wireless recording platform for multinodal neurophysiology in unrestrained naive and parkinsonian rhesus macaques

**Authors:** \***B. POBIEL**<sup>1</sup>, D. L. BAUER<sup>4</sup>, B. MOHANTY<sup>4</sup>, A. VERMA<sup>4</sup>, K. ACEDILLO<sup>6</sup>, N. HJELLE<sup>2</sup>, J. WANG<sup>4</sup>, J. L. VITEK, MD, PHD<sup>5</sup>, L. A. JOHNSON<sup>3</sup>;

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**Abstract:** Understanding the pathophysiology of gait and sleep impairments in Parkinson's disease (PD) remains limited, partly due to the challenge of recording neuronal activity in unrestrained nonhuman primates (NHPs). To address this, we developed a modular 3D-printed housing system and surgical implantation strategy to adapt the Freelynx (Neuralynx, Inc.) wireless neurophysiology recording system for use in rhesus macaques. Our designs enable high-channel-count, high-sampling-rate electrophysiology recordings during natural behaviors such as gait and sleep.

Our approach emphasizes durability and experimental adaptability. The housing minimizes

footprint while protecting the instrumentation during movement and sleep. A custom aluminum bracket dissipates heat, and Omnetics connectors and anchor screws ensure secure and modular probe integration. The design allows for flexible placement of cortical and subcortical electrodes and is compatible with tools such as the FHC STarFix for deep brain stimulation (DBS) targeting.

We achieved up to 12-hour recordings at 30 kHz sampling across 256 channels, capturing activity from the subthalamic nucleus (STN), dorsolateral prefrontal cortex (DLPFC), dorsal premotor cortex (PMc), and motor cortex (MC) in two primates. Recordings spanned full sleep cycles and continuous gait behavior, enabling comparisons across naïve, Parkinsonian, and treatment conditions. Preliminary sleep data suggest that DBS alters cortical and subcortical activity during sleep, supporting its potential for treating sleep disturbances. Gait recordings show specific neuronal modulation during movement.

Our platform balances requirements of battery life, high channel count for simultaneous Utah arrays and DBS lead stimulation and recordings, though size and weight remain considerations. Future refinements include distributed battery configurations and adaptation to percutaneous pedestals.

This platform represents a significant advance in enabling naturalistic, multi-nodal neurophysiology recordings in NHP models of PD, furthering investigations into the neurobiology of gait and sleep. Our design framework could be adapted for other NHP users for their specific purposes, facilitated by our freely shared modular designs.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.14/D30

**Topic:** C.03. Parkinson's Disease

**Support:** P50NS123109  
R01NS131371  
R01NS110613

**Title:** Effect of STN-DBS on cortical neuronal activity during slow-wave sleep in parkinsonism

**Authors:** \***J. YOU**, A. VERMA, K. ACEDILLO, N. HJELLE, B. MOHANTY, J. WANG, C. D. MACKINNON, M. HOWELL, J. L. VITEK, MD, PHD, L. A. JOHNSON;  
Dept. of Neurol., Univ. of Minnesota, Minneapolis, MN

**Abstract:** Slow-wave sleep (SWS) dysfunction is a common non-motor symptom in Parkinson's disease (PD). Given its reported association with cognitive impairment, disease progression and impact on quality of life, there is an urgent need to develop more effective treatment options. Subthalamic nucleus (STN) deep brain stimulation (DBS) is an effective therapy for PD motor signs and can have beneficial impacts on sleep, although the mechanisms of this improvement are unclear. Previous studies have suggested that excessive beta oscillations (8-30 Hz) in the basal ganglia-cortical network during sleep could contribute to SWS dysfunction in PD. In this study, we aim to investigate the effects of therapeutic STN-DBS on cortical neuronal activity and test the hypothesis that DBS-induced improvement in SWS would be associated with reduced cortical beta oscillations during sleep. A nonhuman primate (female, age: 23) was rendered parkinsonian via low-dose (0.2-0.3mg/kg) injections of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Neural recordings (including local field potentials (LFPs), single unit and multi-unit activity) were acquired wirelessly at 30kHz sampling rate (FreeLynx, Neuralynx Inc.) from a 96-ch Utah array (Blackrock) in the dorsolateral prefrontal cortex (DLPFC). Data was recorded overnight in the animal's home enclosure during DBS-ON (n=6) and DBS-OFF (n=5) conditions. Spectral analysis of cortical LFP was performed on an epoch-by-epoch basis (10-sec long epochs). SWS and wake epochs were identified based on DLPFC delta (0.5-4 Hz) power. During SWS in the DBS-OFF condition, we found two distinct oscillatory activities in the beta band, with peak frequency centered at 8 Hz and 17 Hz. STN-DBS was associated with increase in the duration (% of night recording) of SWS ( $39.4 \pm 4.1\%$  vs  $24.2 \pm 3.7\%$ ,  $p < 0.01$ ) and reduction in the duration of nighttime wakefulness ( $25.1 \pm 5.2\%$  vs  $40.8 \pm 2.7\%$ ,  $p < 0.01$ ). DBS-induced improvement in SWS was associated with reduction in peak power at 8 Hz ( $0.16 \pm 0.02$  vs  $0.09 \pm 0.01$ ,  $p < 0.01$ ) but an increase in peak power at 17 Hz ( $0.03 \pm 0.005$  vs  $0.047 \pm 0.005$ ,  $p < 0.01$ ). Our findings suggest that STN-DBS can facilitate consolidation of SWS and reduction in insomnia. However, the neural mechanism (i.e., reduction in 8 Hz power but an increase in 17 Hz power) underlying DBS associated improvement in SWS raises an intriguing question about the functional role of beta oscillatory activity in SWS. This study is a critical step towards understanding the mechanisms by which STN-DBS can improve SWS. Further studies are warranted to decipher the functional roles of distinct beta oscillatory activities in SWS.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.15/D31

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant P50NS123109  
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NIH Grant R01NS037019

**Title:** Characterizing the effects of dopaminergic medication and DBS lead location on pallido-cortical beta coherence in Parkinson's disease

**Authors:** \*N. D. PERERA<sup>1</sup>, B. MOHANTY<sup>1</sup>, K. J. O'NEILL, III<sup>1</sup>, S. L. ALBERICO<sup>1</sup>, M. HILL<sup>1</sup>, D. L. BAUER<sup>1</sup>, J. FROULA<sup>1</sup>, D. P. DARROW<sup>2</sup>, M. C. PARK<sup>2</sup>, L. A. JOHNSON<sup>1</sup>, J. WANG<sup>1</sup>, J. L. VITEK, MD, PHD<sup>1</sup>, J. E. AMAN<sup>1</sup>;

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**Abstract:** Coherent neural activity in the beta range between the globus pallidus internus (GPi), sensorimotor cortical regions (motor (M1) and somatosensory (S1) cortex) has been identified as a potential biomarker in Parkinson's disease (PD). Its presence and response to levodopa, however, is far less studied compared to beta oscillations within individual cortical and subcortical regions. Here, we characterize oscillatory power in the GPi and M1/S1, as well as subcortical-cortical coherence in people with PD, how these measures modulate with levodopa and whether subcortical-cortical coherence has a spatial topography within the GPi.

**METHODS:** Two PD patients were implanted with segmented DBS leads in the right GPi and subdural high-density electrocorticography (ECoG) strips over M1 and S1 regions. Both patients were subsequently externalized for neural recordings. All DBS and ECoG data were processed by referencing to a bipolar montage, removing line noise and bandpass filtering at 1-500 Hz. The power spectra were calculated using the Welch method. GPi-cortical beta coherence was calculated as the area under curve (AUC) of beta band (8-30 Hz) in the coherence spectra. DBS lead and ECoG locations were identified registering preoperative MRIs to a postoperative CT and reconstructed in Slicer.

**RESULTS:** Patient A exhibited a decrease of M1 and increase of S1 beta power on medication compared to off. Conversely, patient B showed an increase of M1 and unchanged S1 beta power. Although one patient demonstrated minimal beta power in the off-medication state, both showed beta suppression in GPi with levodopa. GPi-M1 and GPi-S1 beta coherence was decreased in both patients in the on-medication state compared to off. With respect to location, DBS contacts showing the largest decrease in coherence from off to on medication were posterior and medial facing and coincided with the DBS contacts showing the largest magnitude of beta. Additionally, in both patients the contact chosen for clinically therapeutic stimulation overlapped with the DBS contacts demonstrating the largest magnitude of GPi-M1 coherence in the off state and the largest modulation with medication.

**CONCLUSIONS:** In this study, we show that GPi-cortical beta coherence may be a more reliable neurophysiological biomarker compared to cortical or subcortical beta oscillations alone. Furthermore, we show that beta coherence could be spatially localized within the GPi. These findings demonstrate a potentially reliable circuit-based biomarker that could be useful for intraoperative adjustments of targeting, predicting optimal contacts/subregions for stimulation or adaptive closed-loop DBS algorithms.

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## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.16/D32

**Topic:** C.03. Parkinson's Disease

**Support:** NIH NINDS 1P50NS123103-01 (Emory Udall Research Center)  
NIH P51-OD011132 (Emory National Primate Research Center)

**Title:** Projection- and region-specific firing alterations in the motor cortex of parkinsonian macaques

**Authors:** \***J. TANIMURA**<sup>1,2,3</sup>, **D. PITTARD**<sup>1,2,3</sup>, **O. SOLÍS CASTREJÓN**<sup>4</sup>, **M. MICHAELIDES**<sup>4</sup>, **T. WICHMANN**<sup>1,2,3</sup>, **A. GALVAN**<sup>1,2,3</sup>;

<sup>1</sup>Emory Natl. Primate Res. Ctr., Atlanta, GA; <sup>2</sup>Dept. of Neurology, Sch. of Med., <sup>3</sup>Udall Ctr. of Excellence for Parkinson's Dis. Res., Emory Univ., Atlanta, GA; <sup>4</sup>Natl. Inst. on Drug Abuse, Baltimore, MD

**Abstract:** Parkinson's disease (PD) alters firing rates and patterns of basal ganglia neurons, but its impact on motor-cortical output remains unclear. Previous extracellular recording studies suggested that corticospinal tract neurons (CSNs, identified via antidromic stimulation) in the primary motor cortex (M1) may be strongly affected by the induction of parkinsonism (Pasquereau et al., 2011). Here we examined how projection identity (CSNs vs others) and cortical region (SMA vs M1) differently shape neuronal firing alterations in PD, using opto-tagging. We conducted awake extracellular recordings during spontaneous activity in four rhesus macaques, first in the normal and then in the MPTP-induced parkinsonian state, using 16 or 32-channel silicon probes. Three monkeys received spinal-cord injections of AAV2rg-ChRmERa for optical tagging of CSNs, with its expression confirmed by F18-fluoroestradiol PET scans. In our preliminary analysis, SMA neurons (26 and 47 neurons in the normal and parkinsonian state, respectively) showed firing alterations in the parkinsonian state, with increased inter-spike

interval (ISI) irregularity ( $\Delta$  MAD/median = +0.09 [95% CI: 0.01 to 0.16]), reduced proportion of time spent bursting ( $\Delta$  = -4.2% [-6.7 to -1.6]), and decreased spikes per burst ( $\Delta$  = -2.4 spikes [-4.4 to -0.4]). The instantaneous firing rates contained greater  $\beta$ -band (13-30 Hz) power ( $\Delta$  = +1.3% [0.2 to 2.4]). In M1, we have thus far identified 19 opto-tagged CSNs among 247 M1 units (normal state only). Compared to untagged neurons, CSNs fired faster ( $\Delta$  = +4.6 spikes/s, CSN – untagged [1.6 to 7.8]) and with a more regular pattern ( $\Delta$  ISI MAD/median = -0.16 [-0.24 to -0.08]). Their bursts were shorter ( $\Delta$  = -182 ms [-339 to -16]), with a higher intra-burst rate ( $\Delta$  = +11.8 spikes/s [0.7 to 24.2]). The instantaneous firing rates contained greater power in the  $\beta$ -band ( $\Delta$  = +0.87% [0.05 to 1.67]). The findings suggest that SMA neurons fire less regularly, with less intense bursting, and greater  $\beta$ -band power in the parkinsonian state, compared to the normal state. We also found that M1 tagged CSNs are distinct from unidentified neurons both in firing rate and pattern. Studies of the effects of MPTP on M1 neurons and of opto-tagged SMA neurons are underway. Our opto-tagging approach will clarify projection-specific parkinsonism-associated changes in SMA and M1, helping to elucidate how pathogenic basal ganglia input disrupts cortical output.

**Disclosures:** J. Tanimura: None. D. Pittard: None. O. Solís Castrejón: None. M. Michaelides: None. T. Wichmann: None. A. Galvan: None.

## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.17/D33

**Topic:** C.03. Parkinson's Disease

**Support:** R01NS130551 (NIH/NINDS)  
P51-OD011132 (NIH support to ENPRC)

**Title:** Evaluating ion channel-based chemogenetic modulation of the internal globus pallidus in normal and parkinsonian monkeys

**Authors:** \*D. PITTARD<sup>1</sup>, X. HU<sup>1</sup>, C. ARMSTRONG<sup>1</sup>, O. SOLÍS CASTREJÓN<sup>2</sup>, M. MICHAELIDES<sup>2</sup>, T. WICHMANN<sup>1,3</sup>, A. GALVAN<sup>1,3</sup>;

<sup>1</sup>Emory Natl. Primate Res. Center, Emory Univ., Atlanta, GA; <sup>2</sup>Biobehavioral Imaging and Mol. Neuropsychopharm. Unit, Natl. Inst. on Drug Abuse Intramural Res. Program, Baltimore, MD;

<sup>3</sup>Dept. of Neurol., Emory Univ. Sch. of Med., Atlanta, GA

**Abstract:** Parkinson's disease (PD) is marked by progressive and debilitating motor deficits, driven in part by increased and altered firing patterns within basal ganglia (BG) output nuclei, specifically the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata. Chemogenetic tools have been used to modulate neuronal activity in parkinsonian rodent and non-human primates (NHPs), but chemogenetic manipulation of BG output in NHP models of PD remains unexplored. We hypothesized that targeted reduction of overactive BG

output could alleviate some of the motor signs of parkinsonism, similar to the effects of pallidotomy, an accepted clinical treatment of parkinsonism in humans. In this study, we used a novel ion channel-based platform for chemogenetic modulation, the PSAM/uPSEM system, to inhibit neuronal activity in the GPi of rhesus monkeys ( $N = 3$ ) and tested its impact on progressive parkinsonian motor signs. We performed single bilateral injections of AAVs to express inhibitory PSAMGlyR4 receptors in GPi. Post-mortem data in two monkeys (separate from those in this study) demonstrated very strong expression of the receptors in the BG. We are exploring the use of F18-ASEM PET scans to monitor the expression of PSAMGlyR4 in vivo. We first examined the effects of PSAM activation in normal monkeys, while the monkeys performed an arm reaching task following administration of the effector molecule uPSEM817 (0.064 mg/kg). Then, monkeys were treated weekly with systemic MPTP injections to develop moderate parkinsonism. In the healthy state of one monkey, our preliminary data showed that uPSEM817 administration modestly reduced reaction time ( $209 \pm 131$  (mean  $\pm$  SD) ms), compared to no treatment ( $244 \pm 134$  ms). In one moderately parkinsonian monkey we found that uPSEM817 reduced movement time ( $164 \pm 75.4$  ms) and increased movement velocity ( $0.11 \pm 0.03$  m/s), compared to saline injections ( $222 \pm 111$  ms and  $0.08 \pm 0.03$  m/s, respectively). These preliminary findings suggest that PSAM-mediated inhibition of GPi can modulate movement, but the potential therapeutic impact on parkinsonism motor signs remains inconclusive. Further investigation on the use of this chemogenetic tool for treatment of parkinsonism in NHP models is warranted.

**Disclosures:** D. Pittard: None. X. Hu: None. C. Armstrong: None. O. Solís Castrejón: None. M. Michaelides: None. T. Wichmann: None. A. Galvan: None.

## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.18/D34

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant R01- NS122226-01  
DoD Grant PD230123P2  
The Center for Development and Behavioral Neuroscience at Binghamton University

**Title:** Assessing raphe-striatal vesicular glutamate transporter 3 in levodopa-induced dyskinesia

**Authors:** \*J. A. NARDIELLO<sup>1</sup>, C. BUDROW<sup>3</sup>, C. R. BISHOP<sup>2</sup>;  
<sup>2</sup>Psychology, <sup>1</sup>Binghamton Univ., Binghamton, NY; <sup>3</sup>Behavioral Neurosci., SUNY - Binghamton Univ. Behavioral Neurosci., Binghamton, NY

**Abstract:** Parkinson's disease (PD) is a progressive movement disorder characterized by dopamine (DA) cell loss in the substantia nigra pars compacta (SNc). While levodopa (L-DOPA)

remains the gold-standard treatment, persistent use often results in L-DOPA-induced dyskinesia (LID), typified by involuntary movements and dystonia. Accumulated evidence implicates maladaptive hyperinnervation of the raphe-striatal serotonin (5-HT) system in LID pathophysiology, where dorsal raphe nucleus (DRN) neurons are capable of co-releasing DA, yet the presence of the vesicular glutamate (GLUT) transporter 3 (VGLUT3) in 5-HT neurons suggests a complex interplay with GLUT. This study investigated the role of 5-HT-VGLUT3 co-expression in LID. Transgenic TPH2-Cre<sup>+</sup> Long Evans rats (N=20; M=10, F=10) received unilateral 6-hydroxydopamine lesions and three weeks thereafter all animals received DRN-targeted infusions of CRE-dependent adeno-associated virus encoding green-fluorescent-protein (FLEX-AAV9-GFP) as a tracer, and thereafter assigned to equally lesioned groups based on motor testing. Four weeks post-transduction, rats received daily subcutaneous L-DOPA (n=10; 6 mg/kg) or vehicle (n=10), with abnormal involuntary movements (AIMs) and motor performance assessed on days 1, 7, and 14. After the last day of testing, rats were transcardially perfused and striatal, SNc, and DRN coronal sections were collected for structural analysis via immunohistochemistry (IHC) and double-label immunofluorescence (IF). Behaviorally, L-DOPA treatment in 6-hydroxydopamine-lesioned rats improved motor performance, coinciding with increased LID. Prospectively, we expect tyrosine hydroxylase IHC will confirm lesion severity while IF will reveal treatment-induced changes in VGLUT3 and GFP with increased striatal 5-HT hyperinnervation and VGLUT3 co-localization in the LID-expressing rats. Such structural changes may reflect a novel convergence of presynaptic GLU, 5-HT, and DA function from raphe-striatal 5-HT neurons that drives enhanced postsynaptic activation, aggravating LID. These findings underscore the complexity of 5-HT hyperconnectivity driving aberrant striatal signaling, suggesting VGLUT3 as a potential neuromodulatory target to mitigate dyskinesia in PD.

**Disclosures:** J.A. Nardiello: None. C. Budrow: None. C.R. Bishop: None.

## **Poster**

### **PSTR210: Parkinson's Disease: Bridging Circuit Mechanisms and Interventions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR210.19/D35

**Topic:** C.03. Parkinson's Disease

**Support:** I01RX003676

**Title:** Neurophysiological response and connectivity changes in the STN with a month-long exercise intervention

**Authors:** \*P. JOSHI<sup>1</sup>, L. SHIGO<sup>5</sup>, B. SMITH<sup>5</sup>, C. KILBANE<sup>2</sup>, A. GUHA<sup>1</sup>, A. SINHA<sup>3</sup>, K. LOPARO<sup>3</sup>, A. L. RIDGEL<sup>6</sup>, A. G. SHAIKH<sup>4</sup>;

<sup>1</sup>Biomed. Engin., <sup>2</sup>Dept. of Neurol., <sup>3</sup>Inst. for Smart, Secure and Connected Systems, <sup>4</sup>Case Western Reserve Univ., Cleveland, OH; <sup>5</sup>Exercise Physiol., Kent State Univ., Kent, OH; <sup>6</sup>Kent State Univ., Kent, OH.



**Abstract:** *Background:* Parkinson's disease (PD) affects over 1 million individuals in the United States, presenting significant challenges in symptom management. Current treatment strategies include pharmacological approaches such as levodopa and dopamine agonists, surgical interventions like deep brain stimulation (DBS), and rehabilitative methods such as physical therapy and exercise. While extensive research has explored the effects of levodopa and DBS on basal ganglia circuits, particularly the subthalamic nucleus (STN), the impact of exercise on STN activity remains largely unexplored. Understanding these neural mechanisms underlying these interventions is crucial for optimizing PD management.

*Methods:* This study examines the changes in the STN activity during a month-long exercise intervention with a motorized stationary interactive bike. Along with motor symptoms, we recorded local field potentials (LFPs) from 29 electrodes in 18 STNs of 9 participants using the Medtronic Percept system. LFP spectral features such as 1/f noise, peak oscillatory power, and power in canonical frequency bands alpha (8-12 Hz), low-beta (13-20 Hz), high-beta (21-35 Hz) were studied separately for the electrodes location in the dorsal and ventral part of STN. We also examined the connectivity changes between dorsal and ventral STN locations in response to exercise using the phase slope index (PSI) and imaginary part of coherence (iCOH). Both acute and long-term analysis was performed.

*Results:* While acute changes in STN activity were minimal, long-term analysis revealed a progressive increase in dorsal STN activity over the course of the intervention. iCOH analysis indicated enhanced coherence between dorsal and ventral STN regions in the high-beta range over time. However, a low PSI ( $< 0.1$ ) suggested minimal directional interaction, implying the presence of two distinct oscillatory sources. This observation pointed to a potential hidden driver influencing both regions. To investigate this, we applied a novel computational method—System Structure (SStr)—to assess causal interactions between dorsal and ventral LFPs before and after the intervention. The analysis confirmed the presence of a hidden driver modulating both regions.

*Significance:* Unlike levodopa and DBS, which primarily suppress beta-band activity, exercise was found to enhance STN activity progressively with each session, while concurrently improving motor symptoms. The connectivity analysis suggests that exercise engages distinct neural mechanisms, potentially involving broader network-level responses, and may complement existing PD therapies through a unique mode of action.

**Disclosures:** P. Joshi: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.01/D36

**Topic:** C.03. Parkinson's Disease

**Title:** Enhancer AAVs for the treatment of motor deficits in Parkinson's disease

**Authors:** \*A. FRASER<sup>1</sup>, A. CHOWDHURY<sup>2</sup>, T. L. DAIGLE<sup>3</sup>;

<sup>1</sup>Allen Inst. for Brain Sci., Seattle, WA; <sup>3</sup>Mol. Genet., <sup>2</sup>Allen Inst. For Brain Sci., Seattle, WA

**Abstract:** Treating Parkinson's disease (PD) with levodopa (L-DOPA) becomes less effective with long term use. This is potentially due to progressive nigrostriatal degeneration resulting in reduced production of aromatic l-amino acid decarboxylase (AADC), a rate-limiting enzyme in dopamine synthesis. To therapeutically combat this, L-DOPA doses must be increased over time, but this eventually induces L-DOPA Induced Dyskinesias (LIDs). Applying a gene therapy strategy to target AADC has the potential to provide long-term clinical benefits for PD treatment. To determine if focusing on cell type specificity in delivering AADC may improve the efficacy of L-DOPA treatment and reduced LIDs, we generated enhancer-based AAVs to systemically target relevant cell populations with low off-target expression. We evaluate our therapeutic approach in two mouse models of PD: the 6-hydroxydopamine (6-OHDA) lesion model and the MCI genetic model, using both direct dorsal striatal injection and retro-orbital administration, and assess their motor function in multiple behavioral paradigms. Our results demonstrate that pan-MSN-specific AADC delivery improves motor deficits at lower L-DOPA doses and avoids the adverse effects associated with expression driven by a ubiquitous CMV promoter, regardless of route of administration. Our work provides strong proof-of-concept data supporting enhancer-AAVs as potential circuit-selective therapy for PD, offering a non-surgical alternative to achieve equal or greater therapeutic benefits.

**Disclosures:** A. Fraser: A. Employment/Salary (full or part-time): Allen Institute. A. Chowdhury: A. Employment/Salary (full or part-time): Allen Institute. T.L. Daigle: A. Employment/Salary (full or part-time): Allen Institute.

## Poster

### PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.02/D37

**Topic:** C.03. Parkinson's Disease

**Title:** Circuit specific gene therapy reverses core symptoms in a primate Parkinson's disease model

**Authors:** \*Y. CHEN<sup>1,2</sup>, Z. LU<sup>3</sup>;

<sup>1</sup>MIT, Cambridge, MA; <sup>2</sup>Shenzhen Inst. of Advanced Technol., Shen, China; <sup>3</sup>Basic Sci., Shenzhen Inst. of Advanced Technol., Shenzhen, China

**Abstract:** Parkinson's disease (PD) is a debilitating neurodegenerative disorder. Its symptoms are typically treated with levodopa or dopamine receptor agonists, but their lack of specificity due to the broad distribution of dopamine receptors leads to severe side effects after long-term use. Here, we report the development of a gene therapy strategy to selectively manipulate PD-

affected circuitry. Targeting striatal D1 medium spiny neurons (MSNs), whose activity is chronically suppressed in PD, we engineered a therapeutic strategy comprised of a highly efficient novel retrograde AAV, promoter elements with strong D1-MSN activity, and a chemogenetic effector allowing precise D1-MSN activation after systemic ligand administration. Application of this therapeutic approach rescues locomotion, tremor, and motor skill defects in both mouse and primate models of PD, supporting the feasibility of targeted circuit modulation tools for the treatment of PD in humans. To reduce potential biosafety concerns, we developed a fully humanized DREADD, hM3Ds, and demonstrated its capacity to rescue parkinsonian motor phenotypes after targeted expression in the D1-MSNs. Currently, we are also conducting GLP toxicity studies to prepare for clinical testing of the safety and efficacy of our circuit gene therapy strategy.

**Disclosures:** Y. Chen: None. Z. Lu: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.03/D38

**Topic:** C.03. Parkinson's Disease

**Support:** 1R01NS122226-01

**Title:** Regional Effects of Citalopram on Motor Performance and L-DOPA-Induced Dyskinesia in a Rat Model of Parkinson's Disease

**Authors:** \*E. VALLE, J. HUANG, G. MCMANUS, C. R. BISHOP;  
Psychology, Binghamton Univ., Binghamton, NY

**Abstract:** Parkinson's Disease (PD) is a neurodegenerative movement disorder characterized by the loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc), resulting in the hypokinetic motor symptoms including bradykinesia, muscle rigidity, and tremors. DA replacement with the drug L-3,4-dihydroxyphenylalanine (L-DOPA) remains the gold standard treatment for the motor symptoms of PD. While highly effective at restoring motor ability in the early stages of the disease, within 10 years of chronic treatment with L-DOPA, up to 90% of PD patients will develop a debilitating syndrome characterized by abnormal involuntary movements (AIMs) called L-DOPA-induced dyskinesia (LID). The mechanisms underlying the development and expression of LID are complex, but accumulating research from our lab and others has strongly implicated a role of aberrant neuroplasticity within raphe-striatal serotonin (5-HT) circuits. The serotonin transporter (SERT) and the 5-HT 1A receptor (5-HT1AR) have been identified as antidyskinetic targets as SERT has been shown to have affinity for DA uptake and modulate dysregulated DA in pro-dyskinetic circuits while 5-HT1AR stimulation can autoregulate 5-HT neuronal activity. Indeed, prior work has shown that selective serotonin

reuptake inhibitors (SSRIs) citalopram, fluoxetine, and paroxetine attenuate AIMs when systemically co-administered with L-DOPA in animal models of PD. Therefore, the goal of the current study is to investigate the regional effects of citalopram administered via intra-raphé, intra-striatal, or systemic infusions on LID and motor performance. To do this, adult male Sprague Dawley rats were rendered hemiparkinsonian via a unilateral 6-hydroxydopamine (6-OHDA) lesion to the left medial forebrain bundle. A subset of rats was also implanted with cannulae situated above the dorsal raphe nucleus (DRN) or the striatum ipsilateral to the lesion. All animals were then rendered dyskinetic with 7 days of L-DOPA treatment (12 mg/kg; s.c.) Counterbalanced coadministration testing began on day 8 with L-DOPA (6 mg/kg; sc) and systemic (5 mg/kg, s.c.) or intracerebral citalopram (0, 3 or 10 µg) after which rats were evaluated for AIMs and motor efficacy. Preliminary results have supported the ability of citalopram to effectively reduce LID without sacrificing the motor benefits of L-DOPA though unique contributions to these effects have emerged in a region-dependent manner.

**Disclosures:** E. Valle: None. J. Huang: None. G. McManus: None. C.R. Bishop: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.04/D39

**Topic:** C.03. Parkinson's Disease

**Support:** MB-28-2019  
2021.00643.CEECIND  
2022.13323.BD  
2022.12292.BD  
2022.12641.B  
2023.03466.BD  
UIDB/50026/2020

**Title:** Neuromodulatory Strategies for Parkinson's Disease: Exploring N-acetylcysteine and MRI-Guided Ultrasound for Targeted Neuroprotection and Brain Circuit Modulation

**Authors:** \*R. CARIDADE<sup>1,2</sup>, B. ARAÚJO<sup>1,2,3,4</sup>, C. FERREIRA<sup>5,1,3,4</sup>, C. TEIXEIRA<sup>1,2</sup>, C. GUEDES<sup>1,6</sup>, R. WADE-MARTINS<sup>7,8</sup>, H. J. FERNANDES<sup>7,8</sup>, F. TEIXEIRA<sup>1,2</sup>;

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Genetics, Univ. of Oxford, Oxford OX1 3QX, Oxford, United Kingdom; <sup>8</sup>Kavli Inst. for Nanoscience Discovery, Univ. of Oxford, Dorothy Crowfoot Hodgkin Building, South Parks Road, Oxford OX1 3QU, Oxford, United Kingdom

**Abstract:** Parkinson's disease (PD) is marked by progressive dopaminergic neuron (DAn) degeneration, for which current therapies offer only symptomatic relief. Hence, there is a critical need for novel neuroprotective approaches. Drug repurposing provides a promising route, with N-acetylcysteine (NAC)—a potent antioxidant—emerging as a candidate for reducing oxidative stress and dopamine-induced toxicity. Prior data from our group have shown that NAC restores dopamine transporter (DAT) levels in PD models. Nonetheless, the precise mechanisms through which NAC provides potential disease-modifying properties still require clarification. Moreover, NAC's low bioavailability (9.1%) and limited accessibility to PD-affected brain areas pose a significant problem due to the blood-brain barrier (BBB). MRI-guided focused ultrasound (FUS) can transiently open the BBB, enabling targeted drug delivery. Thus, using an established striatal 6-hydroxydopamine (6-OHDA) rat model of PD, we implemented two distinct therapeutic strategies. Firstly, five weeks after the lesion, NAC was administered orally for seven consecutive days (12000 mg/kg, n = 12/group). After treatment, motor and non-motor behaviors, basal ganglia circuit functionality, and microglial response were assessed to evaluate the therapeutic relevance of NAC. As a second task, leveraging the same 6-OHDA model, NAC was administered intravenously (2 weeks, 50 mg/kg, n = 8/group). MRI-guided FUS was performed to reversibly open the BBB and expose potential topological (re)organizations of PD brain functional networks. Here, motor and non-motor functions were assessed. Moreover, structural, functional, and metabolite quantifications were evaluated using MRI to observe changes in the rat brain. Statistical analyses were used to compare treatment outcomes, including t-tests, two-way ANOVA analysis, and mixed-design factorial ANOVA. Oral NAC monotherapy did not significantly reverse behavioral deficits but exerted neuroprotective effects in midbrain regions (e.g., substantia nigra, ventral striatum, olfactory tubercle;  $p < 0.0001$ ) and modulated glutamatergic circuits (striatum, thalamus, subthalamic nucleus;  $p < 0.05$ ). Modifications in microglia were also observed. FUS-enhanced NAC delivery improved biodistribution and modulated behavior ( $p < 0.05$ ) and revealed distinct structural and metabolic changes in the brain. These findings suggest that NAC holds promise as a disease-modifying agent in PD. Importantly, MRI-guided FUS presents a promising strategy for overcoming BBB limitations, thereby opening new avenues for targeted therapeutic delivery in neurodegenerative diseases.

**Disclosures:** R. Caridade: None. B. Araújo: None. C. Ferreira: None. C. Teixeira: None. C. Guedes: None. R. Wade-Martins: None. H.J. Fernandes: None. F. Teixeira: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.05/Web Only

**Topic:** C.03. Parkinson's Disease

**Support:** Funded by CONAHCYT grant: Ciencia de Frontera (CF-2023-G-133)  
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CONAHCYT-Mexico (2022-000002-01NACF-04257)

**Title:** Synergistic neuroprotective effects of probiotics and blueberries in a 6-OHDA-induced model of hemiparkinsonism in rats

**Authors:** S. CUEVAS CARBONELL<sup>1</sup>, I. I. ARANDA-GONZÁLEZ<sup>2</sup>, L. MARTINEZ MENDIETA<sup>3</sup>, I. PARRA<sup>3</sup>, \*J. L. GONGORA-ALFARO<sup>4</sup>;

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**Abstract:** Parkinson's disease (PD) is the second most common neurodegenerative disorder. While its exact cause remains unclear, evidence suggests that inflammation and oxidative stress play a central role in its pathogenesis. There are no therapies that significantly delay its progression; nonetheless, probiotics and bioactive substances from berries have shown potential in reducing neuroinflammation and protecting dopaminergic neurons. Here, we assessed whether the combination of probiotics and blueberries exerts a synergistic neuroprotective effect in a 6-OHDA-induced hemiparkinsonism in rats. Three groups of male Wistar rats (n = 8-9) were orally treated once daily for 5 wk with a probiotic mix (PROB) containing *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12, each at a dose of  $1 \times 10^9$  CFU; freeze-dried *Vaccinium corymbosum* blueberries (BB) with polyphenols content equivalent to 900 mg/kg of gallic acid, or their combination (BB+PROB). Starting the 3rd wk, the neurotoxin 6-hydroxydopamine (6-OHDA, 8.75 µg/3.5 µL) was injected into the right striatum. Control groups were: sham-lesioned (SHAM) and 6-OHDA-lesioned without treatment (6-OHDA-WT). Motor performance was assessed weekly in the narrow beam walking test, measuring traversal speed and the number of paw slips. Brains were subsequently fixed and coronal striatal sections were processed for tyrosine hydroxylase and Iba1 immunohistochemistry to quantify the extent of dopaminergic fiber loss and the microglial activation, respectively. BB, PROB, and BB+PROB treatments did reduce dopaminergic denervation ( $p < 0.0001$ ; 1-way ANOVA) and microglial recruitment ( $p < 0.0001$ ; Kruskal-Wallis) compared to the 6-OHDA-WT group. BB+PROB elicited greater dopaminergic preservation than BB alone ( $p < 0.05$ ; Tukey) and reduced microgliosis compared to the 6-OHDA-WT group ( $p < 0.001$ ; Dunn). In the narrow beam test, BB+PROB treatment reduced post-lesion bradykinesia compared to 6-OHDA-WT and BB groups ( $p < 0.05$ ; 2-way repeated measures ANOVA, Tukey), and both groups receiving probiotics had fewer motor deficits than the BB alone ( $p < 0.05$ ; 2-way repeated measures ANOVA) or the 6-OHDA-WT group ( $p < 0.05$ ; Tukey). The extent of denervation in the striatum correlated positively (Pearson) with the magnitude of bradykinesia ( $p < 0.05$ ) and paw slips ( $p < 0.001$ ). The combination of probiotics and blueberries had a synergistic effect, preserving dopaminergic innervation, reducing microglial inflammation and improving motor function more than BBs alone compared to 6-OHDA-WT. These results suggest that a diet with both probiotics and blueberries could reduce PD risk or delay its progression.

**Disclosures:** S. Cuevas Carbonell: None. I.I. Aranda-González: None. L. Martinez Mendieta: None. I. Parra: None. J.L. Gongora-Alfaro: None.

## Poster

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.06/D40

**Topic:** C.03. Parkinson's Disease

**Title:** The role of dopamine D3 receptors in dopamine dysregulation syndrome in a bilateral 6-OHDA lesion rat model of parkinson's disease

**Authors:** \*N. HAKIMZADEH<sup>1</sup>, C. R. BISHOP<sup>2</sup>, I. DIROSA<sup>3</sup>, N. LIPARI<sup>4</sup>;

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**Abstract:** Parkinson's Disease (PD) is a neurodegenerative disorder characterized by dopamine (DA) loss in the nigrostriatal pathway, causing motor and non-motor dysfunction. DA replacement therapies, such as Levodopa (L-DOPA) and DA receptor agonists, help mitigate PD symptoms. Specifically, D2 and D3 receptor agonists target motor symptoms such as muscle rigidity and bradykinesia, and offer neuroprotective effects with fewer undesirable side effects associated with PD. However, chronic DA therapy can lead to complications including L-DOPA-induced dyskinesia (LID) and DA dysregulation syndrome (DDS). DDS involves impulsive or compulsive behaviors and is thought to be driven by DA-dependent reward mechanisms within the mesolimbic pathway. Our prior work identified reinforcing effects of L-DOPA thus, to elucidate D3-receptor-specific mechanisms of DDS, we assessed the reinforcing effects of the D3 receptor agonist, PD-128907. To investigate, 15 male and 16 female Sprague Dawley rats received a bilateral 6-hydroxydopamine (6-OHDA) or sham lesion to the medial forebrain bundle, or no surgical intervention. We hypothesized that bilateral 6-OHDA lesions would induce motor deficits, subchronic administration of the D3 receptor agonist, PD-128907, would produce LID, and its reinforcing effects would be greatest in subjects with the greatest DA loss. Motor impairment was evaluated using forepaw adjusting steps (FAS) and rotarod tests. The conditioned place preference (CPP) paradigm assessed the reinforcing effects of PD-128907 by comparing time spent in a PD-128907-paired environment to a non-drug-paired environment. The abnormal involuntary movements (AIMs) test was used to assess dyskinesia severity by quantifying axial, limb, and orolingual behaviors after a PD-128907 dose. Our current results showed reinforcing effects of PD-128907 in parkinsonian rats, indicating overlapping mechanisms of motor and reward pathways. Immunohistochemistry (IHC) is expected to reveal reduced tyrosine hydroxylase (TH) and elevated ventral striatal FosB in lesioned subjects, confirming DA loss in the substantia nigra and striatal overactivity. By uncovering the reinforcing effects of D3 receptor agonists, our research can advance the understanding of receptor-specific mechanisms underlying DDS and pave the way for targeted therapeutic strategies for managing DDS in PD patients.

**Disclosures:** N. Hakimzadeh: None. C.R. Bishop: None. I. DiRosa: None. N. Lipari: None.

**Poster**

**PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.07/D41

**Topic:** C.03. Parkinson's Disease

**Support:** University Technology Management Promotion of Kyung Hee University through the Commercializations Promotion Agency for R&D Outcomes, funded by the Ministry of Science and ICT (00453834)  
National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2025-00521066)

**Title:** Weissella CSG has neuroprotective and anti-inflammatory effects in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease mice

**Authors:** \*Y. CHOI<sup>1</sup>, J. KIM<sup>2</sup>, S. LEE<sup>3</sup>, S. PARK<sup>3</sup>, M. OH<sup>3,4</sup>;

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**Abstract:** Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, characterized by both motor and non-motor symptoms resulting from the degeneration of dopaminergic neurons in the substantia nigra of the midbrain. Recent studies have emphasized the role of gut microbiota dysbiosis in PD pathogenesis, thereby highlighting the therapeutic potential of microbiome-based interventions. *Weissella* CSG, a probiotic strain isolated from traditional Korean food as Kimchi, has been known for anti-inflammatory effects in colitis mice; however, its efficacy on PD has not been elucidated. In this study, we discovered the therapeutic effects of CSG in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mice. C57BL6J mice were orally administered CSG starting 3 days before MPTP exposure and continuing until the end of the experiments. Results showed that CSG ameliorated MPTP-induced motor deficits and dopaminergic neuronal loss in the brain. Additionally, CSG decreased neuroinflammation and mitigated colonic inflammation in MPTP-injected mice. CSG also restored gut microbial balance, which was strongly correlated with behavior improvements and histological recovery. These findings suggest that CSG has neuroprotective and anti-inflammatory effects through modulation of the gut-brain axis, supporting its potential as a microbiome-based supplement for PD.

**Disclosures:** Y. Choi: None. J. Kim: None. S. Lee: None. S. Park: None. M. Oh: None.

**Poster**



## **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.08/D42

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant 7R15NS121784-02 Kim (PI)

**Title:** Targeting senescent cells using senolytics attenuates  $\alpha$ -synuclein pathology in PD

**Authors:** \*D. K. VERMA<sup>1</sup>, Y. KIM<sup>2</sup>;

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**Abstract:** Parkinson's disease (PD) progression is closely linked to the pathological aggregation of  $\alpha$ -synuclein ( $\alpha$ -syn) and age-related glial dysfunction. Recent evidence implicates cellular senescence in glial cells as a key driver of impaired  $\alpha$ -syn clearance and neuroinflammation. This study aims to elucidate the mechanistic relationship between glial senescence and  $\alpha$ -syn preformed fibril (PFF) mediated PD pathology to explore the potential application of senolytic as a therapeutic intervention for PD. Utilizing adult (12-month-old) C57BL/6 mice, we stereotactically injected PFF into the striatum bilaterally and assessed the behavioral changes until obvious symptoms of PD were observed. A senolytic compound, ABT-263 was gavaged for 5 days in a row to induce apoptosis to senescent cells. Biological variables, including age, sex (both male and female), and treatment status (vehicle vs. ABT-263), were rigorously controlled and analyzed to ensure translational relevance. Behavioral analysis revealed motor deficit/dysfunction and impaired motor coordination after PFF injection. Temporal dynamics of  $\alpha$ -syn accumulation, glial senescence markers, and neuroinflammatory profiles were accessed when mice turned 17-month-old, by which we found that ABT-263 significantly restored the motor dysfunction. Immunohistochemical analyses revealed that dopaminergic neuronal loss in the SNc and striatum derived from  $\alpha$ -syn PFF induced protein aggregation was aligned with morphological changes in GFAP-positive astrocytes and Iba1-positive damage-associated microglia. In the follow-up Western blot analysis, senescent glial populations included senescent or reactive phenotypes, such as elevated levels of C3, p21 and p53, which contribute to neuroinflammation, ultimately leading to cell death in  $\alpha$ -synucleinopathies. Importantly, pharmacological ablation of senescent cells using ABT-263 significantly reduced  $\alpha$ -syn burden, normalized glial senescence markers, and attenuated neuroinflammation in PFF injected mice. These findings established that  $\alpha$ -syn PFF-induced glial senescence impaired proteostasis and perpetuated neuroinflammation, thereby exacerbating  $\alpha$ -syn pathology. Targeting senescent glia with senolytic agents represents a promising therapeutic strategy to restore glial homeostasis and mitigate PD progression.

**Disclosures:** D.K. Verma: None. Y. Kim: None.

**Poster**

## **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.09/D43

**Topic:** C.03. Parkinson's Disease

**Support:** The Ministry of Science and Technology of Taiwan, ROC, Grant NSTC 112-2314-B-016-068-MY3  
Medical Research Project grants TSGH\_C04\_114040  
The National Defense Medical Center, ROC grants MND-MAB-C08-114030

**Title:** Neuroprotective and Therapeutic Effects of Sustained-Release PT320 on Depression-Like Behavior in a Mouse Model of Parkinson's Disease

**Authors:** K.-Y. TSENG<sup>1</sup>, T.-T. KUO<sup>2</sup>, P.-K. CHANG<sup>3</sup>, L. OLSON<sup>4</sup>, B. J. HOFFER<sup>5</sup>, \*Y.-H. CHEN<sup>1</sup>;

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**Abstract:** Background: Nonmotor symptoms are early indicators of Parkinson's disease (PD). Recent studies highlight the role of BDNF in these symptoms. PT320, a sustained-release GLP-1 receptor agonist, has emerged as a promising treatment candidate. Methods: We investigated the effects of PT320 on nonmotor symptoms in MitoPark (MP) mice, a progressive PD model. Two treatment paradigms were tested: an early intervention protocol from weeks 5 to 20 and a late intervention protocol from weeks 15 to 20. Results: PT320 administration, whether initiated before or after the onset of nonmotor symptoms, significantly ameliorated depression-like behaviors in MP mice at clinically relevant doses. Early treatment improved dopamine release in the nucleus accumbens (NAc), an effect not observed with late treatment. Furthermore, early PT320 administration markedly increased the expression levels of Akt, phosphorylated Akt, CREB, phosphorylated CREB, and BDNF proteins in the NAc. Genetic analyses further revealed that the neuroprotective effects of PT320 are associated with upregulation of BDNF and its receptor TrkB. Conclusion: PT320 effectively improves nonmotor symptoms in PD, and this effect may be mediated by BDNF signaling pathways.

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### **Poster**

## **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.10/D44

**Topic:** C.03. Parkinson's Disease

**Support:** NIH R01NS110398

**Title:** Putaminal Cav1.3-shRNA gene therapy in aged parkinsonism male and female macaques restores parkinsonian behavioral deficits and demonstrates evidence of nigrostriatal dopamine-phenotype restoration

**Authors:** \*K. STEECE-COLLIER<sup>1</sup>, J. STANCATI<sup>2</sup>, A. SAVANI<sup>1</sup>, S. MULLER<sup>4</sup>, T. J. COLLIER<sup>3</sup>, M. CAULFIELD<sup>5</sup>, M. VANDER WERP<sup>1</sup>, Y. CHU<sup>4</sup>, I. M. SANDOVAL<sup>6</sup>, J. KORDOWER<sup>7</sup>, F. P. MANFREDSSON<sup>6</sup>;

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**Abstract:** We have demonstrated that MRI-guided delivery of adeno associated virus (AAV)-Cav1.3-short hairpin (sh)RNA to the putamen of aged parkinsonian nonhuman primates (NHPs) can decrease expression of dysfunctional Cav1.3 channels, reverse long-standing parkinsonian motor deficits 'OFF' medication, enhance motor response to levodopa, and provide near complete prevention of levodopa-induced dyskinesias (PMID:40437755). Recent studies exploring possible mechanisms that may underlie these unprecedented therapeutic benefits suggest that our RNA-interference (RNAi) therapeutic may provide neuroregenerative efficacy to injured nigrostriatal dopamine (DA) neurons. Specifically, in our model, monkeys first receive the neurotoxin MPTP into the right common carotid artery which induces rapid, extensive primarily unilateral death of DA neurons in the RIGHT substantia nigra (SN). Two weeks later they receive weekly intravenous MPTP (0.15-0.6 mg/kg) which results in bilateral parkinsonian motor signs (2-6 months). However, DA neurons in the LEFT SN subjected to systemic dosing show less rapid/less complete cell death, often demonstrating downregulation of the DA synthetic enzyme tyrosine hydroxylase (TH) in the absence of/prior to cell death. A further feature of our study is that AAV is well-known for retrograde transduction. Indeed, we observe AAV-Cav1.3-shRNA retrograde transport from putamen to the SN that appears to provide restoration of the DA-phenotype (i.e., TH-immunoreactivity) in subpopulations of presumably quiescent DA neurons in the left SN, those that had lost their TH-phenotype but were not overtly killed by MPTP. Despite similarities in TH-fiber denervation in the left putamen, especially post-commissural, AAV-Cav1.3-shRNA recipient monkeys have significantly more TH-ir neurons in the left SN compared to their right SN, and compared to left and right SN in AAV-SCR-shRNA controls. Further, we have recent evidence suggesting that the left SN DA neurons have restored DA function indicated by elevated/normalized DA transporter (DAT) levels in the left putamen despite continued sparsity of putaminal TH. The potential benefit of AAV-Cav1.3-shRNA in SN DA neurons derives from the fact that these neurons have autonomous pacemaking properties mediated by Cav1.3 Ca<sup>2+</sup> channels resulting in excessively high metabolic demands implicated in their vulnerability to neurodegeneration in PD. Thus, it is reasonable to suggest that retrograde transduction of SN DA neurons with our potent Cav1.3 RNAi-based vector could restore

physiological balance, promote restoration of the DA phenotype and lead to restoration of motor function.

**Disclosures:** **K. Steece-Collier:** A. Employment/Salary (full or part-time): Michigan State University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH R01NS110398. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CavGene Therapeutics, Inc. **J. Stancati:** None. **A. Savani:** None. **S. Muller:** None. **T.J. Collier:** None. **M. Caulfield:** None. **M. Vander Werp:** None. **Y. Chu:** None. **I.M. Sandoval:** None. **J. Kordower:** None. **F.P. Manfredsson:** A. Employment/Salary (full or part-time): Barrow Neurological Institute. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH R01NS110398. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CavGene Therapeutics, Inc.; Vector Therapeutics; Neuralina Therapeutics.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.11/D45

**Topic:** C.03. Parkinson's Disease

**Support:** NIH-NINDS (R21NS130370)

**Title:** Aav-driven overexpression of mic60 prevents rotenone-induced parkinsonism in rats

**Authors:** \***M. TRAVIS**<sup>1</sup>, A. OTERO<sup>2</sup>, S. E. GOMBASH LAMPE<sup>3</sup>, K. S. BANKIEWICZ<sup>4</sup>, T. G. HASTINGS<sup>5</sup>, V. VAN LAAR<sup>1</sup>;

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**Abstract:** Parkinson's disease (PD) is a progressive neurodegenerative movement disorder that affects approximately 1 million people in the United States. Currently, there are no available treatments for PD that address the underlying pathophysiology or arrest degeneration. While the specific causes of PD are still unknown, mitochondrial dysfunction is known to contribute to neurodegeneration in PD. Previous work has linked the mitochondrial protein Mic60, which operates as a nexus for regulating mitochondrial homeostasis and cellular stress response, to PD pathophysiology. We previously found that loss of available Mic60 increases the vulnerability of neurons to PD-linked stressors, while increased Mic60 expression is neuroprotective. Therefore,

we are exploring the therapeutic potential of boosting Mic60 via gene therapy to address neuron loss in PD. To do so, 8-10-month-old male (n=27) and female (n=29) rats received a unilateral infusion of AAV2-huMic60 or AAV2-Empty into the substantia nigra. Six weeks post-infusion, rats randomly received daily injections of either rotenone or vehicle to induce a Parkinsonian phenotype. Behavioral assessments included cylinder and postural instability testing. In male rats who received rotenone, Mic60 overexpression preserved postural stability and partially ameliorated rotenone-induced weight loss. Mic60 overexpression partially preserved postural stability in rotenone-treated female rats. Histological assessment of brain tissue shows partial preservation of tyrosine hydroxylase positive neurons in the substantia nigra pars compacta neurons in AAV2-Mic60/rotenone treated animals. These data suggest that the AAV2-driven overexpression of Mic60 is protecting the dopamine neurons in the substantia nigra, preserving motor integrity, and may be a viable treatment for Parkinson's disease.

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## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.12/D46

**Topic:** C.03. Parkinson's Disease

**Support:** Department of Science and Technology, Government of India

**Title:** Design and Development of Ayurveda based food formulation for the treatment of Parkinson's disease

**Authors:** \*R. V R<sup>1</sup>, K. P. MOHANAKUMAR<sup>2</sup>;

<sup>1</sup>Inter Univ. Ctr. for Biomed. Res. and Super Speciality Hosp. (IUCBR & SSH), Kottayam, India; <sup>2</sup>Ctr. for developmental and ageing research, Inter Univ. Ctr. for Biomed. Res. and Super Specilaity Hosp., Kottayam, India

#### **Abstract: Background**

*Mucuna pruriens* (*Mp*) seeds are a natural source of L-DOPA, the precursor of dopamine, and traditionally used in *Ayurvedic* medicine for managing Parkinson's disease (PD). **Aims**

This study was conducted with the following objectives:

- To develop food-based formulations (e.g., biscuits, breads) combining *Mp* seed flour,
- To characterize the formulations and quantify the L-DOPA contents retained post-processing,
- To evaluate the therapeutic potential of these formulations through *in vitro* and *in vivo* evaluations, using neuronal cell lines and PD mouse model. **Methods**

Biscuits were prepared using a dough with *Mp* seed flour and wheat flour. L-DOPA content in raw seed powder, processed formulations, and in the brain tissues from control and MPTP-

treated mice (fed with *Mp* biscuits) was measured using HPLC with electrochemical detection. Parkinsonian motor behaviours and striatal dopamine levels were evaluated in control and MPTP-treated mice. **Results**

L-DOPA was found to be thermally stable, as the baked food products retained L-DOPA content comparable to that of the raw *Mp* seed flour. Feeding of *Mp*-based biscuits to both control and MPTP-treated mice led to elevated striatal dopamine levels and improvement in PD-associated motor behaviours. **Conclusion**

We report here that, (i) *Mp*-based food formulations effectively retained L-DOPA after baking, (ii) oral administration of these formulations significantly restored striatal dopamine levels in MPTP-treated mice, and therefore we surmise that (iii) such formulations can serve as a practical and palatable means for dosing *Mp Ayurveda* medication for managing PD symptoms in elderly patients.

**Disclosures:** R. V r: None. K.P. Mohanakumar: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.13/D47

**Topic:** C.03. Parkinson's Disease

**Support:** South Texas Undergraduate Research Opportunities Program  
NIH Training Grant R25NS115552  
NIH Training Grant T32NS082145  
Geriatric Research Education and Clinical Center (GRECC)

**Title:** Aldehyde dehydrogenase deficiency impairs social interaction preference before locomotor function

**Authors:** P. PEREZ<sup>1</sup>, J. JOHNSON<sup>1</sup>, P. B. STEWART<sup>1</sup>, K. CANTU<sup>1</sup>, E. MAKINSI<sup>1</sup>, N. JOY<sup>1</sup>, J. E. SCHULTZ<sup>1</sup>, E. FERNANDEZ<sup>2,3</sup>, \*G. G. GOULD<sup>1</sup>;

<sup>1</sup>Physiol., <sup>2</sup>Pharmacol. and Barshop Inst., UT Hlth. San Antonio, San Antonio, TX; <sup>3</sup>Geriatric Research, Education, and Clin. Centers, South Texas Veterans Admin., San Antonio, TX

**Abstract:** In Parkinson's disease, nigrostriatal dopamine neurons are lost over time leading to severe motor dysfunction and psychiatric symptoms such as social withdrawal. As the disease progresses, people develop speech impediments from loss of speech motor regions and/or cognitive impairments in language centers. What remains unclear is if impaired dopamine signaling from loss of nigrostriatal pathways is sufficient to attenuate social motivation. There is some evidence supporting this hypothesis from optogenetic studies in mice. To focus at a more fundamental level on the role that dopaminergic neurodegeneration in the nigrostriatal pathway, typical of Parkinson's disease may play in shaping social cognitive function, we utilized an

impaired biogenic aldehyde detoxification mouse model. When dopamine is metabolized in neurons, the intermediate metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL) is a toxic aldehyde normally metabolized by aldehyde dehydrogenase (ALDH) enzymes. Our hypothesis was that DOPAL induced damage would impair social interaction behavior in mice before motor impairment symptoms would be evident. To study this, we generated Aldh1a1 x Aldh2 double knockout (DKO) mice, which have previously been shown to have elevated DOPAL and 4-hydroxynonenal (4-HNE) content that comes before impairments in motor function and loss of midbrain dopamine neurons. Weeks before motor impairments were evident, as measured by exploration of the three-chamber arena, marble burying, social dominance tube test and water T-maze, we observed that DKO mice (N = 26) exhibited reduced preference for social interaction relative to wild-type controls (N = 20) ( $t(29) = 2.2$ ,  $p = 0.04$ ). The discovery was made using a two tailed t-test mean comparison of the time spent in the chamber with a stranger mouse minus time spent in the chamber with a novel object. This finding supports the idea that social withdrawal could be a useful early indicator of nigrostriatal dopaminergic neuron damage due to ALDH deficiency.

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## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.14/D48

**Topic:** C.03. Parkinson's Disease

**Support:** HHMI  
3Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, Houston

**Title:** Examining the effects of GLP-1 receptor agonists in Parkinson's disease reveals functional benefits and reduction in neuroinflammation

**Authors:** \*B. VAIDYA<sup>1</sup>, Y. KIM<sup>2</sup>, Y. LI<sup>3</sup>, H. Y. ZOGHBI<sup>4</sup>;  
<sup>2</sup>Mol. and Human genetics, <sup>3</sup>Mol. Human Genet., <sup>1</sup>Baylor Col. of Med., Houston, TX; <sup>4</sup>Mol. and Human Genet., Baylor Col. of Medicine/HHMI/Jan and Dan Duncan Neurolog. Res. Inst. at Texas Children's Hospital, Houston, TX 77030, Houston, TX

**Abstract:** Glucagon-like peptide 1 receptor (GLP-1R) agonists are increasingly becoming the drug of choice for weight loss in obesity and diabetes. Interestingly, the health benefits of these medications extend beyond disorders affecting weight and metabolism. Studies in patients with obesity suggest that GLP-1R agonists tend to reduce the risk and progression of neurodegenerative disorders such as Parkinson's disease (PD). However, these clinical studies

have provided mixed results with little insight into potential molecular and pathological mechanisms. To address this knowledge gap, we designed a study to examine the effects of GLP-1R agonists in a PD mouse model, the *Sncα*<sup>G51D/G51D</sup> knock-in mouse model, that carries a PD-causing α-Synuclein mutation. This model expresses the mutant allele in the endogenous spatiotemporal pattern and reproduces human PD progression by manifesting the early onset of constipation and loss of olfaction, followed by the development of motor symptoms and dopaminergic loss. We administered two different GLP-1R agonists, Lixisenatide (10 nmol/kg) and Semaglutide (30 nmol/kg), in two cohorts of mice (n=13-15 per drug or saline) using subcutaneous injections for 2 months. We found that both the GLP-1R agonists reversed the early olfaction deficits and constipation at 6 months of age in *Sncα*<sup>G51D/G51D</sup> mice. We are currently ageing the animals to assess motor dysfunction at 9 months of age. The improvements in prodromal symptoms of PD observed at 6 months were accompanied by a decrease in alpha-synuclein accumulation in various brain areas and reduced astrogliosis and microgliosis, as determined using immunofluorescence assays. To further assess the molecular effects of GLP-1R treatment, we performed RNA sequencing on the olfactory bulb and striatum of WT and PD mice that received either saline or GLP-1R agonist treatments. Differential gene expression analysis revealed that Lixisenatide was able to reverse 50% of the disease signatures observed in the PD group in both brain regions, whereas Semaglutide reversed 90% of the disease signatures in the striatum and 30% in the olfactory bulb. GO analysis showed a reduction of inflammatory signalling and astrocyte-related pathways among the rescued genes in both brain regions. In summary, we found that GLP-1R agonists, Lixisenatide and Semaglutide, were effective in rescuing PD-like phenotypes, reducing alpha-Synuclein pathology, and decreasing neuroinflammation.

**Disclosures:** B. Vaidya: None. Y. Kim: None. Y. Li: None. H.Y. Zoghbi: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.15/D49

**Topic:** C.03. Parkinson's Disease

**Support:** Italian Ministry of the University, project ID PRIN 2022 5HJRFX  
Michael J Fox Foundation, project ID MJFF021179

**Title:** Synapsin III modulates alpha-synuclein deposition and its targeting with PK7/Syntacasin halts disease progression in midbrain organoids and a mouse model of Parkinson's Disease

**Authors:** \*G. FAUSTINI<sup>1</sup>, F. LONGHENA<sup>2</sup>, F. AMODEO<sup>1</sup>, V. BREMBATI<sup>1</sup>, E. FRATTINI<sup>3</sup>, M. MAGNI<sup>4</sup>, M. GENNARI<sup>1</sup>, V. STRANIERO<sup>5</sup>, E. VALOTI<sup>5</sup>, M. PIZZI<sup>1</sup>, M. SPILLANTINI<sup>2</sup>, A. DI FONZO<sup>3</sup>, A. BELLUCCI<sup>1</sup>;

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Kingdom; <sup>3</sup>Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy; <sup>4</sup>NEUROLOGIA, Univ. degli Studi di Milano - OSPEDALE POLICLINICO DI MILANO - CENTRO DINO FERRARI, MILANO, Italy; <sup>5</sup>Univ. of Milan, Milan, Italy

**Abstract:** Parkinson's disease (PD) is the most common movement disorder and is characterized by alpha-synuclein (AS) deposition in Lewy bodies (LB) and nigrostriatal dopaminergic neuron degeneration. We recently found that the synaptic protein synapsin III (Syn III) is a new key contributor to PD pathology, as it tightly associates with AS fibrils isolated from post-mortem PD brains and participates in their formation and stabilization (Longhena et al., 2018, 10.1111/bpa.12587; Faustini et al., 2018; Neuropathol 10.1007/s00401-018-1892-1). Other studies revealed that Syn III is markedly accumulated in post-mortem PD brains (Shantaraman et al., 2024, 10.1186/s13024-024-00749-1). We thus developed PK7/Syntacasyn, a small molecule which, by sequestering Syn III from AS fibrillary aggregates, destabilizes and reduces AS pathological aggregation (PCT WO 2022/029151 A1). In this study, we aimed to deepen our understanding on the pathological role of Syn III in PD by addressing whether adeno associated viral vector-mediated overexpression of Syn III in the nigrostriatal system of C57BL/6J mice may result in the onset of PD-like phenotype. In addition, to gain insights on the possible disease-modifying effects of PK7/Syntacasyn in PD, we tested its efficacy in reducing AS aggregation and neuronal degeneration in induced pluripotent stem cells (iPSCs)-derived midbrain organoids (MOs) from PD patients with SNCA multiplications (SNCAm) and human AS transgenic (tg) mice (Faustini et al., 2022, 10.1016/j.ymthe.2022.01.021). We found that Syn III overexpression induced AS aggregation, nigrostriatal dopaminergic terminal damage, inflammatory activation, vascular alterations and led to the development of motility deficits. PK7/Syntacasyn chronic treatment in iPSC-derived SNCAm MOs reduced AS fibrillary deposition and prevented dopaminergic neuron degeneration. Still, 2 months of oral daily administrations of 10 mg/kg PK7/Syntacasyn in human AS tg mice reduced AS fibrillary aggregation, halted nigrostriatal neuron degeneration and restored dopamine release and motility deficits. Our findings indicate that Syn III increase can induce AS pathological aggregation thus leading to a PD-like phenotype. Moreover, they support that PK7/Syntacasyn represents a promising therapeutic strategy to counteract synucleinopathy and slow down dopaminergic neuron degeneration in PD.

**Disclosures:** G. Faustini: None. F. Longhena: None. F. Amodeo: None. V. Brembati: None. E. Frattini: None. M. magni: None. M. Gennari: None. V. Straniero: None. E. Valoti: None. M. Pizzi: None. M. Spillantini: None. A. Di Fonzo: None. A. Bellucci: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.16/D50

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

**Support:** NIH R01-AG08719001A1  
Emory URC 00126307

**Title:** C/ebp $\beta$  Induces motor impairment in the early stage of alzheimer's disease

**Authors:** \*D. HONG<sup>1</sup>, S. S. KANG<sup>2</sup>;  
<sup>1</sup>Emory Univ., Atlanta, GA; <sup>2</sup>Emory Univ., Atlanta, GA.

**Abstract:** Alzheimer's disease (AD) is increasingly recognized to affect motor function even in early disease stages, challenging the traditional view that motor impairment occurs only in advanced AD. The locus coeruleus (LC), the brain's primary source of norepinephrine (NE), projects to motor cortex as well as various brain regions and shows vulnerability in AD pathogenesis. However, mechanism underlying early motor dysfunction in AD progression remains unclear. Here we demonstrate that a CCAAT-enhancer-binding protein (C/EBP $\beta$ ), an inflammation-regulated transcription factor, accelerates the activation of inflammatory cytokines and promotes motor impairment in a transgenic mouse model with neuronal overexpression of C/EBP $\beta$  at a young age. This study aims to examine how neuronal C/EBP $\beta$  and subsequent activation of IL-18 induce LC neurodegeneration, leading to motor impairment in the early stage of AD progression. Employing postmortem brain tissues of AD patients and C/EBP $\beta$  transgenic mice, we confirmed that LC-to-motor cortex noradrenergic pathway integrity is destroyed in both AD patients and C/EBP $\beta$  transgenic mice. Mechanistically, we found that C/EBP $\beta$ -induced IL-18 activation promotes noradrenergic neuronal death, while NE modulates IL-18-induced neuroinflammation through adrenergic receptor signaling. These findings suggest that C/EBP $\beta$  and IL-18 represent promising diagnostic and therapeutic targets for early stage of AD, particularly for identifying and addressing motor dysfunction before widespread cognitive decline.

**Disclosures:** D. Hong: None.

## Poster

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.18/D51

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant

**Title:** Developing Novel immunotherapies Targeting  $\alpha$ -synuclein to Treat Parkinson's Disease

**Authors:** \*G. HEARN<sup>1</sup>, H. YANG<sup>5</sup>, D. REGMI<sup>2</sup>, N. SHEN<sup>2</sup>, K. R. NASH<sup>3</sup>, C. CAO<sup>4</sup>;  
<sup>1</sup>Col. of Arts and Sci., <sup>3</sup>Mol. Pharmacol. and Physiol., <sup>4</sup>Pharmaceut. Sci., <sup>2</sup>Univ. of South Florida, Tampa, FL; <sup>5</sup>Taneja Col. of Pharm., USF Hlth. Taneja Col. of Pharm., Tampa, FL

**Abstract:** • Parkinson's Disease (PD) is a progressive neurodegenerative disorder, clinically identified by motor symptoms such as bradykinesia, tremors, and rigidity, due to dopaminergic neuron loss. A key pathological hallmark of PD is the accumulation of misfolded  $\alpha$ -synuclein in neurons, forming Lewy bodies. Current treatments only manage symptoms; no therapy has been proven to halt disease progression. Given  $\alpha$ -synuclein's central role in PD, it represents a promising target for novel immunotherapies. This study employed a multi-phase experimental design to develop and evaluate novel immunotherapies targeting  $\alpha$ -synuclein in Parkinson's disease. We first generated and screened monoclonal antibodies, identifying one antibody as the most effective due to its high specificity and binding affinity to pathological  $\alpha$ -synuclein. Dendritic cells (DCs) sensitized to  $\alpha$ -synuclein were then prepared, with young mice yielding more viable cells and were tested in wild type mice for safety and effectiveness. These DC vaccines and antibody were then tested in AAV-based PD mouse models. Results showed that both therapies induced strong immune responses, crossed the blood-brain barrier, and improved motor function without causing neuroinflammation. DC vaccination achieved broader brain distribution, while antibody treatment reached higher peripheral concentrations. Ultimately, both approaches promoted neuronal repair and reduced  $\alpha$ -synuclein pathology, supporting immunotherapy as a promising strategy for modifying disease progression in Parkinson's disease. Preclinical research has demonstrated that both vaccine-based and immunotherapeutic strategies exhibit efficacy in animal models of neurodegenerative disorders. Immunotherapy has emerged as a particularly promising avenue for neurodegenerative diseases treatment due to its potential to modulate pathological protein aggregation and neuroinflammation. Our findings provide further evidence supporting the hypothesis that active immunotherapy targeting aggregated  $\alpha$ -Synuclein ( $\alpha$ -Syn) could serve as a viable therapeutic intervention to mitigate the progression of PD symptoms. By rescuing damaged neurons caused by misfolded  $\alpha$ -Syn species and reducing associated neurotoxicity, this strategy holds potential for modifying disease trajectory and improving clinical outcomes in PD patients.

**Disclosures:** G. Hearn: None. H. Yang: None. D. Regmi: None. N. Shen: None. K.R. Nash: None. C. Cao: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.19/D52

**Topic:** C.03. Parkinson's Disease

**Support:** RS-2024-00345742  
RS-2024-00399237  
RS- 2023-00256265  
RS-2021-DD121228  
RS-2022-DD128953

**Title:** Dopamine conjugated Extracellular Vesicles induce autophagy in Parkinson's Disease

**Authors:** \*J. JEONG<sup>1</sup>, J. SUL<sup>1</sup>, S. BAEK<sup>2,1</sup>, Y. CHO<sup>1</sup>, D.-G. JO<sup>1</sup>;

<sup>1</sup>Pharm., Sungkyunkwan Univ., Suwon-si, Korea, Republic of; <sup>2</sup>OPRIMED, Suwon-si, Korea, Republic of

**Abstract:** The application of extracellular vesicles (EVs) as vehicles for anti-Parkinson's agents represents a significant advance, yet their clinical translation is hampered by challenges in efficient brain delivery and complex blood-brain barrier (BBB) targeting strategies. In this study, we engineered dopamine onto the surface of adipose-derived stem cell EVs (Dopa-EVs) utilizing a facile, two-step bioorthogonal click-chemistry approach. This engineering enhanced neuronal uptake of the EVs in primary neurons and neuroblastoma cells. Notably, Dopa-EVs demonstrated increased brain accumulation in mouse models injected with  $\alpha$ -synuclein preformed fibrils ( $\alpha$ -Syn PFF). Therapeutically, Dopa-EVs administration led to the rescue of dopaminergic neuronal loss and amelioration of behavioral deficits in both 6-hydroxydopamine (6-OHDA) and  $\alpha$ -Syn PFF-induced PD models via autophagy induction. These findings collectively indicate that surface modification of EVs with bioorthogonal dopamine presents a potent strategy for targeting dopaminergic neurons in the brain. The remarkable therapeutic potential of Dopa-EVs, demonstrated in PD models, positions them as a highly promising candidate for Parkinson's disease treatment, offering a significant advance over current therapeutic modalities.

**Disclosures:** J. Jeong: None. J. Sul: None. S. Baek: None. Y. Cho: None. D. Jo: None.

## Poster

### PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.20/D53

**Topic:** C.03. Parkinson's Disease

**Support:** LB692 Nebraska Biomedical Research Development Fund  
Dr. George F. Haddix President's Faculty Research Fund (Creighton)  
Health Science Strategic Investment Fund 201038-823260

**Title:** Analysis of CNS-Derived Blood Exosomes for Biomarker Discovery in Parkinson's Disease

**Authors:** \*B. KANG<sup>1</sup>, N. SANDE<sup>1</sup>, H. KIM<sup>1</sup>, J. BAHN<sup>1</sup>, Y. CHAE<sup>1</sup>, M. S. BURNETT<sup>2</sup>, J.-Y. HWANG<sup>1</sup>;

<sup>1</sup>Pharmacol. and Neurosci., <sup>2</sup>Neurol., Creighton Univ. Sch. of Med., Omaha, NE

**Abstract:** Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. PD is caused by the progressive loss of nigrostriatal dopaminergic neurons and is

characterized by increases in cytoplasmic inclusions of alpha-synuclein. Timely diagnosis of PD is critical to providing the proper treatment and care planning, however, current diagnostic laboratory tests for PD are limited. Therefore, identification of reliable biomarkers is clinically imperative. Exosomes are nanovesicles found throughout the body that carry various proteins, mRNAs, and microRNAs. Central nervous system (CNS)-derived exosomes can cross the blood-brain barrier and have been suggested as potential biomarkers in some pilot studies. Thus, research related to a further validation and a large independent cohort study is needed for relevancy and accuracy. To examine the possibility of using CNS-derived exosomes as biomarkers and identify novel candidates, we isolated CNS-derived exosomes from the peripheral blood of PD patients and age-matched healthy controls. The results from Western blot analysis using antibodies against L1CAM and ATP1A3, markers for CNS exosomes, showed that CNS-derived exosomes are successfully isolated from blood. We then examined whether PD-related pathogenic proteins, including Parkin, PINK1, DJ-1, and phosphorylated  $\alpha$ -synuclein are altered in these exosomes. Our findings indicate that a subset of these proteins significantly differ between PD patients and healthy controls, suggesting their potential use as diagnostic biomarkers. To further identify novel candidates, we are currently conducting a proteomic analysis of CNS-derived exosomes. We anticipate this analysis will uncover novel protein biomarkers for the diagnosis of PD.

**Disclosures:** B. Kang: None. N. Sande: None. H. Kim: None. J. Bahn: None. Y. Chae: None. M.S. Burnett: None. J. Hwang: None.

## **Poster**

### **PSTR211: Parkinson's Disease Intervention Strategies Using Novel Therapeutics in Preclinical Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR211.21/D54

**Topic:** D.04. Brain Injury and Trauma

**Support:** Youth Program: Grant No. 2022M723243  
General Program: Grant No. 32400814

**Title:** Behavioral regulation mechanisms of striatal dopamine dynamics post-cell therapy for parkinson's disease

**Authors:** \*Y. ZHOU;

Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China

**Abstract:** Parkinson's disease (PD) is primarily characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to motor dysfunction. Transplanting in vitro-differentiated dopamine cells into the striatum of PD patients is considered a promising therapeutic strategy. However, whether the activities and dopamine release of

transplanted dopaminergic neurons can be regulated by host behaviors remain unclear. In this study, we transplanted human embryonic stem cell-derived midbrain dopamine precursor cells into the striatum of PD model SCID mice. By combining in vivo fiber photometry recording with some different behavioral paradigms, we investigated the activity and dopamine dynamics of the transplanted human midbrain dopaminergic neurons (hmDANs). Our results showed that the activity and dopamine release of hmDANs were modulated in a behavior-dependent manner. Specifically, the DA dynamics were similar to those of the endogenous nigrostriatal circuit during turning and reward behaviors, but differed during running. Further brain slice electrophysiological recordings revealed that the striatal-transplanted hmDANs received direct inhibitory inputs from local Medium spiny neurons (MSNs) evoked by optogenetic stimulation. This inhibitory input primarily influenced the activity and DA dynamics of transplanted hmDANs during running behavior. Our findings confirm that the activity and dopamine release of transplanted hmDANs are dynamically regulated by different behavioral states. It reveals both similar features and differences in behavioral regulation between the reconstructed neural circuits of striatal-transplanted hmDANs and the endogenous nigrostriatal pathway. These findings provide direct evidence that hmDANs can integrate into host circuits in a behaviorally responsive manner, offering new insights into the functional reconstruction of neural pathways in vivo.

**Disclosures:** Y. Zhou: None.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.01/D55

**Topic:** C.06. Neuromuscular Diseases

**Support:** JAXA  
KAKENHI JP18K06510  
Nihon University School of Medicine 50th Anniversary Fund Research Grant (2016)

**Title:** Analysis of gene expression profiles in the spinal cord and dorsal root ganglion of microgravity-exposed mice and ALS model mice

**Authors:** \*M. YOSHIKAWA<sup>1</sup>, M. MATSUKAWA<sup>2</sup>, Y. SUMI<sup>1</sup>, I. TODA<sup>1</sup>, M. UEMURA<sup>1</sup>;  
<sup>1</sup>Osaka Dent. Univ. Sch. of Dent., Osaka, Japan; <sup>2</sup>Nihon Univ. Sch. of Med., Tokyo, Japan

**Abstract:** Exposure to microgravity (MG) and motor neuron diseases like amyotrophic lateral sclerosis (ALS) leads to motor deficits such as muscle wasting and reduced neuronal activity. However, the specific link between MG and ALS-related motor neuron degeneration is unclear. To clarify how each condition affects the motor system, we analyzed the impact of MG and mutant SOD1 on gene expression in various cell types of the mouse spinal cord. Using known

cell-type markers identified in previous single-cell studies, we examined differentially expressed genes (DEGs) in the spinal cords of MG and SOD1 mice. Most cell types, including neurons, astrocytes, oligodendrocytes, oligodendrocyte precursor cells, meningeal cells, microglia, and vascular cells, exhibited extensive DEGs in the MG spinal cord. Overall, DEGs increased with ALS progression. At postnatal day 30 (P30), we observed distinct abnormalities in putative microglia, meningeal cells, and oligodendrocyte precursor cells in the SOD1 spinal cord. We also assessed neuronal populations in the spinal cord. Putative excitatory and inhibitory neurons were affected more than cholinergic neurons in MG and SOD1 mice. MG affected all putative neuron types, particularly visceral motor neurons, and axon initial segments. Neurons and neuronal components in the SOD1 spinal cord were less affected at P30 but showed an increase with age. These findings indicate MG and ALS pathology are non-cell autonomous and involve various cell types in motor neuron degeneration. We also studied the effects of MG and SOD1 mutants on gene expression in multiple cell types of the mouse dorsal root ganglion (DRG). Using known markers from previous studies, we identified the affected putative cell types in the DRGs of MG and SOD1 mice. DEGs were observed in most cell types, including large neurons, medium/small neurons, satellite glial cells, and Schwann cells, in both the MG and SOD1 DRGs. Abnormalities were observed in putative large/medium neurons (NF200, TrkB, and parvalbumin groups) and mechanoreceptors (Mrgpb4 group) in the MG DRG. The SOD1 DRG showed changes in putative medium neurons (TrkB group), mechanoreceptors (Mrgpb4 group), and nociceptors (TRPV1 group). These results suggest that MG and ALS pathology differentially affect various DRG neurons, potentially contributing to motor neuron degeneration.

**Disclosures:** M. Yoshikawa: None. M. Matsukawa: None. Y. Sumi: None. I. Toda: None. M. Uemura: None.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.02/D56

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH Grant 5R25NS090978-08

**Title:** Every neuron counts: “Presymptomatic” disease is defined by restricted behavioral and neural dynamics in a mouse model of SOD1-ALS

**Authors:** \*R. CHOPRA<sup>1</sup>, J. ZHONG<sup>1</sup>, T. M. MILLER<sup>2</sup>, K. B. HENGEN<sup>3</sup>;

<sup>1</sup>Washington Univ. in St. Louis, Saint Louis, MO; <sup>2</sup>Neurol., Washington Univ, Sch. Med., Saint Louis, MO; <sup>3</sup>Biol., Washington Univ. In St. Louis, Saint Louis, MO

**Abstract:** It is widely accepted that neurodegenerative diseases are defined by a “presymptomatic” period of accumulated cellular pathology that transitions to clinical symptoms once the pathology reaches a critical threshold. In the case of amyotrophic lateral sclerosis

(ALS), there is already devastating motor neuron loss at the time of symptom onset, reflecting months to years of undetected disease activity.

One might expect that the first signs of network injury would be detectable at the emergent scale. As the brain's computations directly instruct behavior, behavior should inherit the features of network dynamics, and network dysfunction should be reflected in the dynamics of behavior. We challenge the truism that early network injury is "asymptomatic" and explore the hypothesis that network dynamics and behavioral dynamics collapse at the onset of motor neuron loss. If true, such a finding would transform the landscape of clinical interventions, offering the promise of intervening in "presymptomatic" individuals.

Using a newly-developed homepage for automated phenotyping, we find that B6.CgTg(SOD1\*G93A)Gur/J mice (hereafter hSOD1-G93A mice) display simplification of their motor repertoire starting as early as post-natal day 60 (P60). This coincides with serum markers of neurodegeneration (i.e. neurofilament light chain) but long before the onset of apparent motor impairment by standard behavioral assays. Chronic M1 recordings demonstrate that cortical dynamics progressively shift from an optimal emergent set-point (criticality) within the same timeframe as restricted motor dynamics. Behavioral structure analysis reveals that simplification reflects loss of scale-free structure typically observed in healthy organisms' free behavior.

These findings provide a platform for re-imagining neurodegenerative disease as a two-stage process wherein pauci-symptomatic network injury maintains performance at a cost of flexible computation, followed later by a catastrophic phase of progressive symptoms when network injury is advanced.

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## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.03/D57

**Topic:** C.06. Neuromuscular Diseases

**Title:** Amyloid accumulation, neuroinflammation and loss of motor neurons are the hallmark of a SOD1 rat model of ALS

**Authors:** A. GHAVAMI<sup>1</sup>, S. MONGIA<sup>3</sup>, K. KOVACOVICOVA<sup>3</sup>, A. ZAJICEK<sup>2</sup>, M. OSBORNE<sup>3</sup>, M. JACOBSON<sup>4</sup>, L. GRIFFIN<sup>5</sup>, M. CARR<sup>5</sup>, \*T. HANANIA<sup>6</sup>, D. HAVAS<sup>3</sup>; <sup>2</sup>Rat Pharmacol., <sup>1</sup>PsychoGenics, Paramus, NJ; <sup>3</sup>PsychoGenics Inc, Paramus, NJ; <sup>4</sup>Taconic Biosciences, Inc., Rensselaer, NY; <sup>5</sup>Taconic Biosci., Rensselaer, NY; <sup>6</sup>PsychoGenics, Inc., Paramus, NJ

**Abstract:** Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease which is characterized by muscle weakness, eventual paralysis and death. There is no cure for ALS to date, and existing treatments focus on providing symptomatic relief and improving life



quality. In collaboration with Taconic Biosciences, Inc, PsychoGenics characterized a new rodent model of SOD1 G93A-overexpressing (NTac:SD-Tg(SOD1G93A)L26H) rats. The results have indicated this model to be a valuable tool for researching ALS and developing potential therapies as it replicates many key features of the disease, including motor neuron degeneration, muscle dysfunction, and increased neurofilament light chain (NfL) levels, a biomarker for neurodegeneration. In the current study, we used fixed frozen spinal cord sections derived from approximately 36 weeks old male and female transgenic SOD1 rats and wildtype littermates. Sections were labeled with combination of antibodies to SOD1 *amyloid* [Pentameric formyl thiophene acetic acid (pFTAA) and superoxide dismutase (SOD1)], *inflammatory markers* [Glial Fibrillary Acidic Protein (GFAP) and Ionized calcium-binding adaptor molecule 1 (Iba1)], along with motor neuron markers such as choline acetyl transferase (ChAT) and neuronal nuclei (NeuN). Our data showed significant amyloid accumulation accompanied by an increase in neuroinflammation in the spinal cord of transgenic rats, confirming the disease pathology and associated neuroinflammation. A significant reduction in the number of motor neurons was also detected, however, the overall number of neurons in the spinal cord remained unaltered. Additional work is being done using specific new targets valuable in the field, such as lipid peroxidation and mitochondrial damage, as these have been shown to be implicated in ALS rodent models. In summary, the SOD1 G93A rats show a significant amyloid accumulation, neuroinflammation and a loss of motor neurons in the spinal cord which leads to progressive muscle weakness and eventual paralysis. While the research is still ongoing, these initial findings indicate that this new rat model holds promise as a useful platform for screening potential novel therapeutics.

**Disclosures:** **A. Ghavami:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **S. Mongia:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **K. Kovacovicova:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **A. Zajicek:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **M. Osborne:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **M. Jacobson:** A. Employment/Salary (full or part-time): Taconic Biosciences. **L. Griffin:** A. Employment/Salary (full or part-time): Taconic Biosciences. **M. Carr:** A. Employment/Salary (full or part-time): Taconic Biosciences. **T. Hanania:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **D. Havas:** A. Employment/Salary (full or part-time): PsychoGenics Inc.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.04/D58

**Topic:** C.06. Neuromuscular Diseases

**Title:** Using *C. elegans* to uncover the link between the cellular unfolded protein response and TDP-43 proteotoxicity

**Authors:** \*O. LARA, C. VOISINE;  
Biol., Northeastern Illinois Univ., Chicago, IL

**Abstract:** Neurodegenerative diseases are categorized by deterioration of nerve cells and chronic progression of fatal symptoms. A hallmark of these diseases is the aggregation of specific proteins in affected neurons. TAR DNA Binding Protein 43 (TDP-43) is found in aggregates in several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), and more. Under normal conditions, cells possess an evolutionarily conserved system that prevents protein aggregation called proteostasis. However, in these diseases, this system no longer functions properly. To study the link between proteostasis and TDP-43 related toxicity, we are using the small, transparent nematode, *Caenorhabditis elegans*. The entire genome and nervous system of *C. elegans* have been completely mapped. In the Voisine lab, a transgenic line expressing human TDP-43 expressed in the nervous system has already been generated. Using this transgenic line, I will perform a genetic cross to introduce a deletion of *catp-3* ( $\Delta catp-3$ ), a gene whose product is involved in proteostasis. The unfolded protein response (UPR), a system that is responsible for maintaining proteostasis within the endoplasmic reticulum (ER) by responding to accumulation of unfolded or misfolded proteins, has been shown to affect TDP-43 toxicity. Specifically, treatments acting on the UPR have been seen to improve motor functions and decrease protein aggregates in *C. elegans* and *D. rerio* with TDP-43. Once this new strain is generated, I will examine the physiological effects of disrupting proteostasis of TDP-43 toxicity. Using a well-established behavioral assay called a thrashing assay, I will measure the movement of the worms in liquid to assess motor neuron function. I hypothesize that removing the *catp-3* gene will improve motor neuron function in worms expressing TDP-43. Observing the behavioral effects of  $\Delta catp-3$  would provide insight into the role of proteostasis in neurodegenerative pathology.

**Disclosures:** O. Lara: None. C. Voisine: None.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.05/D59

**Topic:** C.06. Neuromuscular Diseases

**Title:** Early phenotypic characterization of TDP43-Q331K mouse model of ALS reveals elevated plasma neurofilament light, CMAP abnormalities and behavioral deficits.

**Authors:** T. VOGELS, H. PHAM, Z. HARTEMAN, \*M. LOOS;  
InnoSer, Leiden, Netherlands

**Abstract:** TAR DNA binding protein 43 (TDP-43), encoded by the TARDBP gene, is a major pathological protein involved in the pathogenesis of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). TDP43 pathology is observed in 97% of all cases of ALS,

making this protein a major therapeutic target for ALS treatment. In this study, we performed an extensive longitudinal characterization of TDP43-Q331K mice, to assess the progression of disease-relevant phenotypes, with the aim of evaluating the model's suitability for preclinical therapeutic studies. Transgenic male and female TDP43 mice expressing human TDP43 with the Q331K mutation and control mice expressing wild-type (WT) mouse TDP43 protein were examined at early (4, 7, 10 and 13 weeks of age) and females also at older ages (4, 6 and 8 months). Motor function was assessed by a battery of tests (spontaneous behavior in automatic home-cages, inverted grid, weight-lifting test, rotarod, CatWalk test, and grip strength. Nerve conduction was assessed by testing the compound muscle action potential (CMAP). Brains and spinal cords were isolated for histopathology analyses. Blood was collected for neurofilament light chain (NfL) plasma biomarker analysis. Beginning at 4 months, TDP43-Q331K mice displayed deficits in multiple motor domains, including reduced performance in rotarod, weight-lifting, and inverted grid tests. Impaired gait was observed in the Catwalk test at 6 months of age. Spontaneous behavior analysis revealed significantly lower activity duration during dark phase starting at 4 months, as well as significantly lower on-shelter visit during the dark phase at 6 and 8 months, and significantly longer shelter visits at all timepoints of the TDP43-Q331K mice. Principal component analysis of multiple variables in the automated PhenoTyper home-cages showed consistent phenotypes at different ages, with a progressively larger effect size over time. Plasma NfL was increased in the older cohort and is not yet analyzed for the younger cohort. Histopathological analyses for neuroinflammatory markers (Iba1, GFAP) are still ongoing. In conclusion, TDP43-Q331K mice have the first detectable motor symptoms at 4 months of age, as well as increased plasma NfL and impaired nerve conduction. TDP43-Q331K mice are therefore a suitable model to test therapeutics that target the earliest disease signs of ALS and FTD in the TDP43-Q331K mouse model.

**Disclosures:** **T. Vogels:** A. Employment/Salary (full or part-time): InnoSer. **H. Pham:** A. Employment/Salary (full or part-time): InnoSer. **Z. Harteman:** None. **M. Loos:** A. Employment/Salary (full or part-time): InnoSer.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.06/D60

**Topic:** C.06. Neuromuscular Diseases

**Title:** Characterization of an inducible INTRATHECAL TDP43-AAV AMYOTROPHIC LATERAL SCLEROSIS model

**Authors:** \***R. RABL**<sup>1</sup>, **B. KIEN**<sup>4</sup>, **L. BREZNIK**<sup>1</sup>, **M. DAURER**<sup>1</sup>, **L. JAUKE**<sup>5</sup>, **M. LJEKAJ**<sup>1</sup>, **K. PLATTNER**<sup>1</sup>, **A. FANTINA-WOBLISTIN**<sup>2</sup>, **S. FLUNKERT**<sup>3</sup>, **M. PROKESCH**<sup>6</sup>;  
<sup>2</sup>R&D, <sup>3</sup>Neuropharm., <sup>1</sup>Scantox Neuro GmbH, Grambach, Austria; <sup>4</sup>Study Coordination, Scantox Neuro GmbH, Parkring 12, A-8074 Grambach, Austria, Grambach, Austria; <sup>5</sup>Res. & Develop., <sup>6</sup>Discovery, Scantox Neuro, Grambach, Austria

**Abstract:** Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease characterized by degeneration of motor neurons in the brain and spinal cord. The RNA binding protein TDP-43, which aggregates and mislocalizes in ALS patient brains, is a key driver of ALS pathology. Overexpression of TDP-43 *in vitro* and *in vivo* induces ALS pathology and provides a suitable model for studying mechanisms underlying ALS. However, homozygous TDP-43 transgenic mice show a fast progressing and early fatal pathology. For this reason, we aimed to establish an ALS-specific mouse model with moderate progression. For the proposed study, hemizygous mice overexpressing human wild type TDP43 (hTDP-43) under control of a neuronal murine Thy-1 promotor were used. Mice show a 0.6-fold expression of hTDP-43 compared with wild type mice but no ALS-related motor deficits. Adult hemizygous TDP-43 overexpressing mice were therefore intrathecally (IT) injected with an adeno-associated virus 9 (AAV9) carrying human TDP-43 and evaluated for behavioral deficits and electromyographic alterations. At baseline, as well as 6 and 12 weeks after IT injection, animals were longitudinally analyzed for motor deficits using wire suspension test, beam walk test and open field test. Additionally, Compound Muscle Action Potential (CMAP) and Motor Unit Number Estimation (MUNE) were measured by electromyography (EMG). Analysis revealed that animals show a progressive motor phenotype which correlates with a reduction in CMAP and MUNE. The observed behavioral and electromyographic deficits in TDP-43-AAV mice suggest that animals develop a robust phenotype combined with an extended survival time compared to homozygous TDP-43 transgenic mice. TDP-43-AAV mice are thus a valuable model for studying progressive pathological processes and the development of TDP-43-related therapies against ALS and frontotemporal dementia.

**Disclosures:** **R. Rabl:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **B. Kien:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **L. Breznik:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Daurer:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **L. Jauk:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Ljekaj:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **K. Plattner:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **A. Fantina-Woblistin:** 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**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.07/D61

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH 1R21NS124209  
Alzheimer's of Central Alabama (ACA) Lindy Harrell Pre-Doctoral Scholar Award

**Title:** TFE3 nuclear enrichment occurs in neurons vulnerable to TDP-43 pathology

**Authors:** \*S. MOLAEI RAMSHE<sup>1</sup>, H. SIDDIQI<sup>2</sup>, M. S. SIMMONS<sup>3</sup>, A. COOK<sup>2</sup>, R. VAN WAARDENBURG<sup>3</sup>, S. BARMADA<sup>4</sup>, A. E. ARRANT<sup>5</sup>, R. M. COWELL<sup>6</sup>;

<sup>1</sup>Univ. of Alabama at Birmingham, Birmingham, AL; <sup>2</sup>Univ. of Alabama at Birmingham, Birmingham, AL, ; <sup>3</sup>Birmingham, AL, ; <sup>4</sup>Univ. of Michigan, Ann Arbor, MI; <sup>5</sup>Neurol., Univ. of Alabama At Birmingham, Birmingham, AL; <sup>6</sup>Neurol., Univ. Alabama at Birmingham, Birmingham, AL

**Abstract:** MiT/TFE transcription factor family (TFE3, TFEB, MITF, and TFEC) regulates lysosomal and autophagic programs and has gained interest as a therapeutic target in neurodegeneration. However, the consequences of sustained MiT/TFE activation in neurons remains unclear. Using single-cell transcriptomic datasets, fluorescent *in situ* hybridization, and immunostaining, we identified TFE3 as the predominant MiT/TFE factor in neurons across the brain at both RNA and protein levels. In the Thy1-TARDBP (TAR44) mouse model, which overexpresses human TDP-43 and mimics aspects of TDP-43 proteinopathy, we observed region-specific TFE3 overexpression and nuclear enrichment accompanied by lysosomal dysfunction in layer V cortical, hippocampal, and spinal motor neurons, vulnerable cell types in amyotrophic lateral sclerosis and frontotemporal dementia. To our knowledge, this represents the first *in vivo* demonstration of neuronal TFE3 nuclear localization in a neurodegenerative context. To investigate the functional consequences of TFE3 modulations, we bilaterally injected 2-4-month-old C57BL/6J mice with: (1) AAV9-CAG2-FLAG-TFE3 to induce TFE3 overexpression, (2) tamoxifen-inducible AAV9-CAG2-FLAG-TFE3-ERT to drive nuclear enrichment, or (3) AAV9-CAG2-FLAG as control. Neuron-specific expression was confirmed by NeuN co-labeling and lack of IBA1 or GFAP overlap. TFE3 nuclear enrichment was confirmed by DAPI co-staining and nuclear/cytoplasmic quantification using CellProfiler (blinded image analyses). RNA-seq of TFE3-overexpressing hippocampi (n=5/group) revealed upregulation of lysosomal and disease-associated microglia (DAM) genes, with 386 genes shared with differentially expressed transcripts in TAR44 hippocampus (n=4/group), indicating convergence on lysosomal and neuroimmune pathways. These changes occurred despite neuron-specific AAV expression, suggesting neuron-derived inflammatory signaling. TFE3 nuclear enrichment also led to  $\gamma$ H2AX accumulation (a proxy for DNA damage) and abnormal cathepsin D (CTSD) distribution in neurons, consistent with genotoxic and lysosomal stress. Similar  $\gamma$ H2AX elevation was observed in TAR44 layer V neurons with nuclear TFE3, suggesting a link between TFE3 localization and neuronal stress. Although MiT/TFE activity can enhance lysosomal pathways, our findings show that sustained nuclear enrichment of TFE3 fails to prevent lysosomal and DNA damage in the context of TDP-43 pathology and may instead contribute to neuronal stress. These results suggest that therapeutic strategies targeting MiT/TFE factors require precise regulation of timing and cell-type specificity.

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**Poster**

**PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.08/D62

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH 1R21NS124209  
Alzheimer's of Central Alabama (ACA) Lindy Harrell Pre-Doctoral  
Scholar Award

**Title:** Determining the dependence of neurons on the transcription factor TFE3 for lysosomal maintenance and gene expression

**Authors:** \*H. SIDDIQI<sup>1,2</sup>, S. MOLAEI RAMSHE<sup>2</sup>, A. COLAFRANCESCO<sup>2</sup>, M. S. SIMMONS<sup>2</sup>, C. FARMER<sup>3</sup>, K. E. SCHOONOVER<sup>3</sup>, S. A. ANDRABI<sup>2</sup>, R. M. COWELL<sup>2</sup>;  
<sup>1</sup>Albert Einstein Col. of Med., Bronx, NY; <sup>2</sup>Neurol., <sup>3</sup>Psychiatry, Univ. of Alabama at Birmingham, Birmingham, AL

**Abstract:** Many neurodegenerative disorders are characterized by lysosomal dysfunction and the abnormal accumulation of proteins in neurons, leading researchers to propose that programs for lysosomal biogenesis should be activated for neuroprotection. Many considerations are necessary when prioritizing potential drug targets, including the baseline expression of the target (gene/protein) in the appropriate cell types and tissues. The most studied MiT/TFE member is TFEB, but single cell transcriptomic databases suggest it is lowly expressed in neurons. An underexplored MiT/TFE member, TFE3, shows the highest expression in these databases; this study (1) explored TFE3's neuroanatomical and cell type-specific expression profile compared to TFEB and MITF and (2) determined whether mice lacking TFE3 show signs of transcriptional dysregulation and/or lysosomal depletion. Using fluorescence *in situ* hybridization and immunofluorescence, we found that TFE3 is highly abundant in neurons and microglia throughout the brain and spinal cord. Moreover, TFE3 is significantly more expressed than TFEB and MITF in cortical glutamatergic neurons. Next, TFE3's biological role in lysosomal maintenance and gene expression was explored with a whole body TFE3 knockout mouse model. Protein markers for lysosomal quantity (LAMP1 and LAMP2a), function (CTSD), and autophagy (LC3 A/B) were not reduced in hippocampal tissue homogenates or at the single-cell level, suggesting that TFE3 is not required for maintenance of lysosomal pools. However, RNA sequencing revealed changes in several genes, some of which are involved in the maintenance of the Golgi apparatus and trafficking, without changes in lysosomal genes or other MiT/TFE members. These findings propose that at baseline conditions, neurons are not dependent on TFE3 for lysosomal maintenance and gene expression and that other transcription factors could be involved in lysosomal gene regulation. Importantly, stress conditions may be required to evaluate TFE3-mediated transcriptional regulation; initial studies with primary neuronal cultures suggest that TFE3 cytoplasmic to nuclear translocation can be robustly induced with activators of lysosomal stress. Future studies will explore the roles for TFE3 translocation in neurodegenerative disorders, with the goal of determining whether it would be a good candidate for therapeutic targeting.

**Disclosures:** H. Siddiqi: None. S. Molaei Ramshe: None. A. Colafrancesco: None. M.S. Simmons: None. C. Farmer: None. K.E. Schoonover: None. S.A. Andrabi: None. R.M. Cowell: None.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.09/D63

**Topic:** C.06. Neuromuscular Diseases

**Title:** Spatial multiomics mapping of neuroinflammation in a mouse model of Amyotrophic Lateral Sclerosis

**Authors:** C. SAYGILI DEMIR<sup>1</sup>, J. BALLESTEROS ALVAREZ<sup>1</sup>, M. BONNET<sup>1</sup>, S. AUBERT<sup>1</sup>, P. MACHADO ALMEIDA<sup>1</sup>, E. MARTERSTECK<sup>1</sup>, D. WAKHLOO<sup>2</sup>, A. DIKSHIT<sup>3</sup>, \*M. PROCOPIO<sup>1</sup>, S. BRAJKOVIC<sup>1</sup>;

<sup>1</sup>Lunaphore Technologies, Tolochenaz, Switzerland; <sup>2</sup>Bio-Techne, Newark, CA; <sup>3</sup>Advanced Cell Diagnostics, Newark, CA

**Abstract:** The immune response plays an important role in the onset of neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), a disorder characterized by the progressive loss of the motor neurons controlling voluntary muscle contraction (PMID: 30663610). Understanding the spatial immune and structural landscape of the brain is crucial for gaining insight into the complex and poorly understood interactions occurring in the neurodegenerative brain. Here, we employed a multiomics assay combining multiplexed immunofluorescence and RNA in situ hybridization for detecting proteins and RNA biomarkers simultaneously on the same sample, to assess neuroimmune changes in a mouse model of ALS. Fixed-frozen sagittal brain sections from TAR6/6 transgenic mice overexpressing human TAR DNA-binding protein 43 (TDP-43) protein, linked to ALS pathology, were utilized for this study (PMID: 29787578). Tissue sections were stained and imaged using the COMET™ platform, integrating RNAscope™ (PMID: 22166544) HiPlex Pro and multiplexed sequential immunofluorescence (seqIF™, PMID: 37813886) into a fully-automated workflow. This approach enables multiplex detection of up to a 12-plex RNA and 24-plex protein panel on the same section. Images were then analyzed using HORIZON™ software to map the spatial distribution of distinct cell populations and to quantify protein and RNA expression at single-cell resolution.

High-plex proteomic panels enabled mapping of key cell types, including neurons, astrocytes, microglia, oligodendrocytes, and vasculature-associated cells. Transcriptomic targets included markers of neuronal and glial function. Integrating these panels into a single multiomics assay allowed spatial profiling of cell types, detection of immune activation, and characterization of molecular changes in the ALS model. Our tissue-wide analysis revealed region-specific increases in markers of astrogliosis and microgliosis, such as Gfap, Tspo and Cd11c; along with signs of axonal loss and synaptic disruption indicated by a reduction in the mRNA expression levels of

Nf-M, Nf-L andDlg4.

This fully automated multiomics approach enables a detailed look at single-cell resolution into the spatial dynamics of neurodegeneration and neuroimmunity, offering novel insights into the molecular pathology of ALS and the broader mechanisms driving neurodegenerative diseases.

**Disclosures:** **C. Saygili Demir:** A. Employment/Salary (full or part-time): Lunaphore Technologies. **J. Ballesteros Alvarez:** A. Employment/Salary (full or part-time): Lunaphore Technologies. **M. Bonnet:** 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. **E. Martersteck:** 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

### PSTR212: ALS and Motor Neuron Diseases: Animal Models

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.10/D64

**Topic:** C.06. Neuromuscular Diseases

**Title:** Probing the role of *Drosophila* stathmin in stabilizing neuromuscular synapses

**Authors:** \*S. LEE<sup>1</sup>, N. L. TRAN<sup>2</sup>, D. K. DICKMAN<sup>1</sup>;

<sup>1</sup>Neurobio., <sup>2</sup>USC, Los Angeles, CA

**Abstract:** Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by progressive motor neuron loss and neuromuscular junction (NMJ) denervation, ultimately leading to paralysis and death. While genetic studies have implicated several key genes, including *stathmin*, a critical regulator of microtubule dynamics in axons, the precise mechanisms by which *stathmin* dysfunction contributes to NMJ breakdown remain largely unknown. To address this gap in our understanding, we employed a powerful *Drosophila* model to investigate the role of *stathmin* in maintaining NMJ integrity. Our initial studies reveal that the sole *Drosophila stathmin* orthologue is exclusively expressed within the nervous system, highlighting its specific role in neuronal function. Within motor neurons, we are actively characterizing the subcellular localization of Stathmin and examining how cellular stress pathways influence its distribution. Leveraging CRISPR/Cas9-mediated gene editing, we generated new and specific *stathmin* mutant alleles which exhibited severe NMJ degeneration accompanied by significant reductions in the levels of essential synaptic proteins. Furthermore, our preliminary data using confocal and super-resolution microscopy, alongside electrophysiological analyses, is dissecting the key structural and functional consequences of *stathmin* loss at the NMJ, particularly in the context of other factors that compromise NMJ



stability. Collectively, our findings position Stathmin as a critical sensor of axonal stress, acting as a pivotal regulator that integrates degenerative and potentially regenerative signaling pathways to safeguard the stability and functionality of neuromuscular circuits.

**Disclosures:** S. Lee: None. N.L. Tran: None. D.K. Dickman: None.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.11/E1

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH R21NS133927  
NIH R01NS129902  
Simons Collaboration Simons Collaboration on Plasticity and the Aging Brain

**Title:** Cell Type-Specific Mitochondrial Profiling Reveals Intrinsic Properties of Corticospinal Neurons and Novel Mechanisms of Vulnerability in ALS

**Authors:** \*B. A. COTTO<sup>1</sup>, L. ZHANG<sup>1</sup>, B. FAIT<sup>1</sup>, M. RAO<sup>1</sup>, N. HEINTZ<sup>2</sup>, E. F. SCHMIDT<sup>3</sup>;  
<sup>2</sup>Lab. of Mol. Biol., <sup>3</sup>Lab. Mol Biol, <sup>1</sup>Rockefeller Univ., New York, NY

**Abstract:** Neurodegenerative diseases are often characterized by marked anatomical and cellular specificity. Among them, Amyotrophic Lateral Sclerosis (ALS) results from the selective loss of corticospinal neurons in the motor cortex and lower motor neurons in the spinal cord, eventually leading to paralysis and death. Despite significant progress in identifying the genetic and molecular factors involved in ALS, little is known about the exact mechanisms underlying the selective vulnerability of motor neurons. A major unresolved issue is that many ALS-causing gene mutations are ubiquitously expressed throughout the body, yet only a subset of neurons is vulnerable. Mitochondrial dysfunction has emerged as a common and early feature in both familial and sporadic ALS, suggesting an important role for the loss of mitochondrial integrity in the disease's etiology. Previous in vivo studies of ALS-associated mitochondrial dysfunction have predominantly relied on analyses of whole brain or large regions. These approaches are limited by the extensive cellular heterogeneity of the cortex, which can obscure meaningful changes in the rare and vulnerable corticospinal neurons. To address this limitation, we developed and applied a retroAAV-mediated approach, termed TOM-TAG, to enable cell type-specific immunopurification of mitochondria from whole tissue homogenates. This powerful tool facilitates the rapid and precise characterization of mitochondrial properties across specific cell populations in complex tissues like the cortex. Using this strategy in combination with proteomic profiling and real-time metabolic analysis, we identified striking differences in mitochondria isolated from ALS "resilient" versus "vulnerable" neuronal populations, both at baseline and in a relevant animal model. Taken together, our findings indicate intrinsic differences in

mitochondrial physiology between these distinct neuronal populations that may contribute to disease susceptibility.

**Disclosures:** B.A. Cotto: None. L. Zhang: None. B. Fait: None. M. Rao: None. N. Heintz: None. E.F. Schmidt: None.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.12/E2

**Topic:** C.06. Neuromuscular Diseases

**Support:** Laurence and Sandi Gluck Charitable Foundation

**Title:** Investigating mechanisms underlying motor neuron degeneration in a CSF-mediated animal model of sporadic ALS

**Authors:** \*J. K. WONG, S. M. KOVALEV, S. A. SADIQ;  
Tisch MS Res. Ctr. of NY, New York, NY

**Abstract:** Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by motor neuron degeneration. Sporadic ALS (sALS) accounts for 90% of ALS cases in which there is no family history of the disease. We previously found that intrathecal delivery of cerebrospinal fluid (CSF) from sALS patients, but not familial ALS patients, induced motor disability, motor neuron degeneration, and TDP-43 mislocalization in adult wildtype mice (Wong et al., 2022). CSF filtration and proteomic analysis identified apolipoprotein B-100 (ApoB) as the neurotoxic factor in sALS CSF. However, the mechanisms underlying sALS CSF/ApoB-induced motor neuron degeneration have yet to be elucidated. The goals of this study were to: 1) investigate the role of the ApoB receptor, low-density lipoprotein receptor (LDLR), in mediating motor neuron degeneration in sALS, and 2) identify global transcriptomic changes occurring in the spinal cord following exposure to sALS CSF. To determine whether LDLR is necessary for sALS CSF/ApoB-induced neurotoxicity, adult C57BL/6J or LDLR KO mice underwent laminectomies at cervical levels 4 and 5, then received injections into the subarachnoid space delivering 3 $\mu$ L of: 1) saline, 2) sALS CSF, 3) ApoB, 4) sortilin antibody + ApoB, or 5) LDLR antibody + ApoB. Forelimb motor function was assessed at 1 day post injection and mice were perfused for ChAT and TDP-43 immunostaining. All motor and histological assessments were performed blinded. To identify global transcriptomic changes induced by sALS CSF, cervical spinal cords from C57BL/6J mice injected with either sALS CSF or healthy control CSF were processed for spatial transcriptomics analysis using the 10X Genomics Visium HD platform. C57BL/6J mice injected with sALS CSF or ApoB developed significant motor disability and motor neuron loss, which was not observed in C57BL/6J mice injected with LDLR antibody + ApoB, or LDLR KO mice injected with sALS CSF or ApoB. TDP-43 mislocalization was also significantly reduced in LDLR KO mice. Preliminary spatial transcriptomics analysis revealed that sALS CSF induced

significant enrichment of gene sets in motor neurons, including those associated with neurodegeneration, axon degeneration, abnormal axon morphology, and negative regulation of the PI3K/AKT network, which regulates LDLR expression and has previously been implicated in ALS pathology. Together, our data highlight the importance of LDLR in mediating sALS CSF/ApoB-induced neurotoxicity and provide a potential link between LDLR and transcriptomic signatures associated with ALS pathology. Future studies will further explore common signaling pathways connecting LDLR to motor neuron degeneration.

**Disclosures:** J.K. Wong: None. S.M. Kovalev: None. S.A. Sadiq: None.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.13/E3

**Topic:** C.06. Neuromuscular Diseases

**Support:** R21NS128630 to DRS  
R21NS127028 to DRS  
R01NS137233 to DRS  
R01NS097903 to DRS  
R35NS127253 to DRS and SMP  
R61/R33NS124965 to DRS and SMP  
R35NS097275 to NMB

**Title:** Autophagy dysfunction and neurodegeneration in a human Staufen1 BAC mouse

**Authors:** \*D. R. SCOLES<sup>1</sup>, S. PAUL<sup>1</sup>, M. M. GANDELMAN<sup>1</sup>, W. DANSITHONG<sup>1</sup>, K. FIGUEROA<sup>1</sup>, N. M. BONINI<sup>2</sup>, S. M. PULST<sup>1</sup>;  
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**Abstract:** Staufen1 (STAU1) is an RNA binding protein and member of the ATXN2 protein complex that regulates mRNA degradation and subcellular localization. Previously, we found that STAU1 is overabundant in fibroblasts from amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD), as well as in tissues from mouse models of these diseases. STAU1 overabundance disrupts autophagic flux through its direct binding to the 5' UTR of *MTOR*, leading to its increased translation and hyperactivation. STAU1 overabundance and impaired autophagy lead to the accumulation of biomolecular condensates and activation of an abnormal unfolded protein response (UPR), which is normalized by reducing STAU1 expression. In this study, we explored the pathological effects of STAU1 overexpression in mice. We developed a transgenic mouse model carrying a bacterial artificial chromosome (BAC) containing the full human *STAU1* gene. Expression of human *STAU1* was confirmed in the cerebral hemispheres, cerebellum, and spinal cord, as well as in cultured cortical neurons, astrocytes, and microglia

derived from cortex and spinal cord. Markers of autophagy dysfunction were detected in the brain, cerebellum, and spinal cord of BAC-STAU1 mice, and were significantly ameliorated following *STAU1* knockdown via RNA interference. Additionally, in *Drosophila* models expressing TDP-43 or CAG-expanded *ATXN2*, STAU1 dosage influenced the severity of retinal degeneration, and reducing STAU1 expression restored normal phenotypes. Despite these molecular alterations, BAC-STAU1 mice did not exhibit overt neurodegenerative behavior, suggesting that STAU1 acts as an epistatic modifier of neurodegeneration rather than a primary driver. This model provides a valuable tool for preclinical testing of therapies aimed at reducing STAU1 expression.

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## Poster

### PSTR212: ALS and Motor Neuron Diseases: Animal Models

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.14/E4

**Topic:** C.06. Neuromuscular Diseases

**Support:** the Israel Science Foundation (1740/18)  
The French Muscular Dystrophy Association (AFM-Téléthon) (22193 and 24091)

**Title:** A Conditional *Vrk1* Cholinergic Knock Out Mouse is a Model for severe Motor Neuron Degeneration

**Authors:** \*S. GOLAN<sup>1,2</sup>, I. GREENBAUM<sup>1,2</sup>, A. SCHAUDER<sup>3</sup>, S. OREN<sup>3</sup>, Y. ROSENBERG<sup>1,2</sup>, S. BEN-DOR<sup>4</sup>, S. B. MEILIN<sup>3</sup>, E. LEVY-LAHAD<sup>2,1</sup>, P. RENBAUM<sup>2</sup>;  
<sup>1</sup>The Hebrew Univ., Jerusalem, Israel; <sup>2</sup>Shaare Zedek Med. Ctr., Jerusalem, Israel; <sup>3</sup>MD Biosci., Rehovot, Israel; <sup>4</sup>Dept. of Life Sci. Core Facilities, Weizmann Inst. of Sci., Rehovot, Israel

**Abstract:** Mutations in the *VRK1* (Vaccinia-related kinase 1) gene have been implicated in neurodegenerative disease, primarily affecting motor neuron and brain development. However, VRK1's role in motor neuron (MN) survival and underlying disease mechanisms remain poorly understood. In this study, we investigated the role of *Vrk1* in motor neuron disease (MND) by generating a conditional knockout (cKO) mouse model lacking *Vrk1*, specifically in cholinergic neurons. We created a *Vrk1*-targeted Cre-lox MND mouse model, in which Cre recombination resulted in a null mutation of *Vrk1*. Cre recombinase was specifically expressed in cholinergic neurons, including MNs, generating a cholinergic neuron-specific *Vrk1* KO (*Vrk1* ChAT-cKO) mouse model. The phenotype was analyzed by observation, motor activity testing, histological examination and immunostaining. We assessed motor neuron (MN) degeneration, neuromuscular junction (NMJ) denervation, and muscle atrophy in these mice. *Vrk1* ChAT-cKO mice showed progressive motor degeneration, weight loss, reduced grip strength, tail dragging, decreased

mobility, tremors, kyphosis, and respiratory distress, leading to premature death by approximately 27 days. Histological and molecular analysis of spinal cord sections in postnatal day 24-27 cKO mice revealed significant motor neuron degeneration, including vacuolation, chromatolysis, and apoptosis, along with a 40-50% loss of ChAT positive MNs ( $p=0.006$ ). The remaining MNs showed a 36-44% reduction in mean soma size ( $p=0.006$ ). Denervation of NMJs was observed in 60% of the junctions ( $p=0.003$ ), along with abnormal postsynaptic AChR cluster maturation. Muscle atrophy was observed, with a nearly 80% reduction in myofiber area ( $p=0.0004$ ). The *Vrk1 ChAT-cKO* mouse model recapitulates the severe MN phenotype observed in human *VRK1*-related neurodegeneration, underscoring VRK1's critical role in motor neuron integrity. The progressive nature of motor dysfunction, along with NMJ abnormalities and muscle atrophy, suggests that VRK1 is essential for maintaining motor neuron survival and neuromuscular functions. This model offers a valuable tool for studying VRK1-associated MND and could contribute to the development and assessment of therapeutic strategies targeting VRK1 pathways. Additionally, this model may provide insights into the shared mechanisms between MNDs, such as ALS and SMA, and VRK1-associated MND.

**Disclosures:** S. Golan: None. I. Greenbaum: None. A. Schauder: None. S. Oren: None. Y. Rosenberg: None. S. Ben-Dor: None. S.B. Meilin: None. E. Levy-Lahad: None. P. Renbaum: None.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.15/E5

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH/NINDS R01NS113765 to CLL and MAL  
MO Spinal Cord Injury/Disease Research Program (SCIDRP) grant to MAL

**Title:** Early respiratory and swallowing pathology of SMA and SMARD1 mouse models

**Authors:** \*R. MUCHOW<sup>1</sup>, C. SMITH<sup>1</sup>, F. LLORENTE TORRES<sup>2</sup>, D. PEREZ-LOPEZ<sup>1</sup>, N. NICHOLS<sup>1</sup>, M. LORSON<sup>3</sup>, C. LORSON<sup>1</sup>;

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**Abstract:** Spinal muscular atrophy (SMA) is a neuromuscular disease that affects roughly 1 in 10,000 people. It is caused by the loss of the SMN1 gene, which leads to a shortage of SMN protein. This deficiency results in neurodegeneration, muscle mass loss, and muscle weakness. In some cases, people with SMA also experience problems with respiratory and oral function, including difficulty swallowing (dysphagia). A similar condition, spinal muscular atrophy with respiratory distress (SMARD1), is caused by mutations in the IGHMBP2 gene. While SMARD1

patients share many clinical symptoms with SMA patients, the main characteristic of SMARD1 is severe respiratory distress. Both SMA and SMARD1 patients suffer from respiratory and swallowing deficits. While 3 approved drugs dramatically impact patient outcomes in SMA, nearly 40% of patients still report using respiratory support. Despite how crucial these symptoms are, there has been surprisingly little animal model research to understand what causes these significant clinical issues. To better understand the pathways involved in these important hallmarks of disease, we examined SMARD1 and SMA mouse models, respectively: FVB-*Ighmbp2<sup>nmd/nmd</sup>* (FVB-nmd); *Smn<sup>-/-</sup>* SMN2<sup>+/+</sup> SMNΔ7<sup>+/+</sup> (SMNΔ7). In these models there is a reduction of IGHMBP2 or SMN protein. The average lifespan of FVB-nmd mice is 19 days while SMNΔ7 is 14 days. We used plethysmography to examine respiration during normoxia, hypercapnia and hypercapnia + hypoxia. FVB-nmd mice showed respiratory abnormalities in nearly all parameters and have a reduced central drive response. In contrast, SMNΔ7 mice exhibited difficulties with air flow during inspiration and expiration. We analyzed diaphragm and intercostal muscles and found that there were no changes in neuromuscular junction (NMJ) innervation in these muscles in FVB-nmd mice while SMNΔ7 mice showed NMJ denervation only in the internal intercostals. Further examination of the diaphragm showed both mutant models had significantly reduced diaphragm muscle fiber area with no changes in muscle fiber type distribution. Both models show decreased axon size and myelin thickness in the phrenic nerve. As breathing and swallowing are tightly coordinated functions, we also examined oral muscles including the masseter, mylohyoid, genioglossus and geniohyoid. In FVB-nmd mice, we did not observe any significant NMJ denervation of these muscles; however, SMNΔ7 mice showed significant NMJ denervation in these muscles. Overall, we hope to identify specific pathways that contribute to disease progression with respect to respiratory and swallowing defects and determine the differences in pathology between SMA and SMARD1.

**Disclosures:** R. Muchow: None. C. Smith: None. F. Llorente Torres: None. D. Perez-Lopez: None. N. Nichols: None. M. Lorson: None. C. Lorson: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CLL is co-founder and chief scientific officer of Shift Pharmaceuticals.

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.16/E6

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH grant 1R01NS134816-01

**Title:** Characterizing SMARD1 pathogenesis using the *Ighmbp2*<sup>R604X/R604X</sup> patient-derived mutation: insights into disease mechanisms.

**Authors:** \*F. LLORENTE TORRES, R. MUCHOW, D. O. PEREZ-LOPEZ, M. WOOLRIDGE, M. LORSON, C. LORSON;  
Univ. of Missouri, COLUMBIA, MO

**Abstract:** Mutations in the Immunoglobulin mu binding protein 2 (*IGHMBP2*) gene result in two distinct diseases: the rare and severe SMA with Respiratory Distress Type I (SMARD1) or a milder Charcot Marie Tooth Type 2S (CMT2S). There is no clear correlation between type of mutation and disease severity or onset. *IGHMBP2* is an RNA/DNA helicase with proposed functions in many processes including translation. To understand the differences between these two maladies, and the role of *IGHMBP2* in disease pathology, we generated mouse models based on *IGHMBP2* patient mutations. Here, we focus on *Ighmbp2*<sup>R604X/R604X</sup> mice, which serve as a potential promising SMARD1 disease model. SMARD1 is a neuromuscular disorder characterized by early-onset respiratory distress, progressive distal to proximal muscle atrophy and autonomic nervous system defects. Without ventilatory support patients die within the first year of life. The R605X mutation (R604X in mice) is located within the *IGHMBP2* helicase domain. Our biochemical studies show that *IGHMBP2*-R605X protein has significantly reduced biochemical activity. In our characterization of *Ighmbp2*<sup>R604X/R604X</sup> mice and when compare with wild type littermates as controls, we found a significant reduction in lifespan (median survival 6 days) and weight. Interestingly, we did not see significant differences in latency to fall assessments. Quantitative plethysmography was used to measure respiration, a key clinical symptom of SMARD1, and at P3 *Ighmbp2*<sup>R604X/R604X</sup> mice had significant respiratory differences. Diaphragm neuromuscular junction (NMJ) innervation status was consistent between wild type and *Ighmbp2*<sup>R604X/R604X</sup> mice; however, there was a significant decrease in diaphragm muscle fiber area in *Ighmbp2*<sup>R604X/R604X</sup> mice. The phrenic nerve in *Ighmbp2*<sup>R604X/R604X</sup> mice showed significant reductions in axon area, diameter, myelin thickness and G-ratio. Nerve conduction (sciatic nerve) and muscle response (gastrocnemius) was measured using electrophysiology. Distal latency and repetitive nerve stimulation were significantly increased in *Ighmbp2*<sup>R604X/R604X</sup> mice while P-P and O-P CMAP amplitude and negative area were significantly decreased. Consistent with these studies, *Ighmbp2*<sup>R604X/R604X</sup> sciatic nerve axon area, diameter, myelin thickness and G-ratio were all significantly decreased. Significant NMJ denervation of the gastrocnemius and tibialis anterioris muscles and reduction in muscle fiber area were also observed. These studies provide significant insight into SMARD1 disease pathology and *IGHMBP2* function and establishes a new platform to evaluate mechanistic questions and preclinical therapies.

**Disclosures:** F. Llorente Torres: None. R. Muchow: None. D.O. Perez-Lopez: None. M. Woolridge: None. M. Lorson: None. C. Lorson: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shift Pharmaceuticals Inc..

## **Poster**

### **PSTR212: ALS and Motor Neuron Diseases: Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.17/E7

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH 1R01NS113765  
State of MO/Univ of MO Spinal Cord Injury/Disease Research Program

**Title:** Understanding the function of the IGHMBP2-ABT1 interaction and its role in SMARD1/CMT2S

**Authors:** \*S. C. HURT<sup>1</sup>, G. VADLA<sup>1</sup>, K. SINGH<sup>1</sup>, C. LORSON<sup>2</sup>, M. LORSON<sup>3</sup>;  
<sup>1</sup>Univ. of Missouri - Columbia, Columbia, MO; <sup>3</sup>Vet. Pathobiology, <sup>2</sup>Univ. of Missouri, Columbia, MO

**Abstract:** Immunoglobulin mu-binding protein 2 (IGHMBP2) is an RNA/DNA helicase. Mutations in the *IGHMBP2* gene give rise to two neuromuscular disorders: Spinal Muscular Atrophy with Respiratory Distress type I (SMARD1) and Charcot-Marie-Tooth disease type 2S (CMT2S). SMARD1 is characterized by early-onset diaphragmatic paralysis leading to respiratory failure and premature death. CMT2S is a milder condition with progressive limb weakness and sensory deficits, but without respiratory involvement. Despite the shared genetic origin in *IGHMBP2*, the specific cellular mechanisms disrupted in these diseases remain unclear. No effective treatments exist. Our previous work identified activator of basal transcription 1 (ABT1) as an IGHMBP2-interacting protein and modifier of SMARD1 pathology, that modulates IGHMBP2 biochemical activity. It is unknown if the absence of the IGHMBP2-ABT1 interaction is associated with SMARD1/CMT2S disease pathology. We showed pathogenic *IGHMBP2* mutations, D565N, R605X, and H924Y, exhibit altered ABT1 binding and biochemical activity consistent with disease severity and pathology in the respective *Ighmbp2* mutant mice. To further elucidate the IGHMBP2-ABT1 interaction, we generated IGHMBP2 C-terminal deletions associated with patient mutations and analyzed IGHMBP2-ABT1 binding and IGHMBP2 biochemical activity. We also expressed tagged wild-type and mutant IGHMBP2 along with wild-type ABT1 in HEK293 cells to examine how these mutations affect the IGHMBP2-ABT1 association and localization through immunohistochemistry and co-immunoprecipitation analyses. This includes deletion mutants that move stepwise through the protein to further understand which domains of IGHMBP2 are necessary for ABT1 binding. To examine the extent that these IGHMBP2 mutants rescued disease pathology, we introduced viral vectors expressing these *Ighmbp2* deletion constructs by intracerebral ventricular (ICV) injection into the FVB-*Ighmbp2*<sup>nmd/nmd</sup> mouse model, which exhibits reduced IGHMBP2 levels. These studies report our in vitro and in vivo findings concerning the IGHMBP2-ABT1 interaction, how pathogenic IGHMBP2 mutations alter this interaction, and their effects on IGHMBP2 biochemical activity and disease pathology.

**Disclosures:** S.C. Hurt: None. G. Vadla: None. K. Singh: A. Employment/Salary (full or part-time): Adnexus Biotechnologies. F. Consulting Fees (e.g., advisory boards); 21st Solutions LLC. C. Lorson: A. Employment/Salary (full or part-time): Shift Pharmaceuticals. M. Lorson: None.

**Poster**

**PSTR212: ALS and Motor Neuron Diseases: Animal Models**



**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR212.18/E8

**Topic:** C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

**Support:** NIH Grant RM1 STING  
NIH Grant 1RF1NS127407

**Title:** Using proteasome inhibition to model TDP-43 phenotype in mice

**Authors:** \*V. S. VILLARREAL, P. SENARATNE, M. YATES, C. MARQUES, B. J. WAINGER;  
Neurol., Massachusetts Gen. Hosp., Charlestown, MA

**Abstract:** TDP-43 is a ubiquitously expressed nuclear RNA binding protein that regulates RNA processing. TDP-43 pathology, including the loss of nuclear TDP-43 and its accumulation in cytoplasmic aggregates, is present in half of patients with Alzheimer's Disease, half of patients with the related frontotemporal dementia, and 97% cases of amyotrophic lateral sclerosis. Despite its importance, the underlying mechanisms by which TDP-43 contributes to disease remain incompletely understood, particularly the relative involvement of loss-of-nuclear function and gain-of-cytoplasmic toxicity. Current animal models rely on genetic mutation, overexpression, or knockdown of TDP-43, and thus incompletely model these different contributions. Recent findings suggest that proteasome inhibition—a form of cellular stress that disrupts protein homeostasis—can induce TDP-43 mislocalization in vitro, offering a promising non-genetic strategy to model ALS pathology. Here, we present a novel model for TDP-43 proteinopathy induced by proteasome inhibition and demonstrate the therapeutic potential of drugs identified in an in vitro screen to restore physiological TDP-43. We administered proteasome inhibitors longitudinally to adult mice. Histological analysis reveals hallmark features of ALS pathology including loss of nuclear TDP-43 in spinal cord and motor cortex, as well as reduction in the number of ChAT+ motor neurons in the ventral horn of the spinal cord with prolonged administration. In behavioral assays, we observe reduction in motor function. Treatment with small molecule hits mitigates the model findings on both the pathological and behavioral levels. Taken together our data hold promise for the application of a new mouse model of TDP-43 proteinopathy in which the TDP-43 locus or levels are not directly perturbed. Our data also support the robustness of findings across cellular and animal models, in that hits from a small molecule screen in iPSC neurons yield concordant benefit in the developed mouse model.

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**Poster**

**PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.01/E9

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Sex differences in lipopolysaccharide-induced sickness and anhedonia in mice are in part associated with  $\alpha 5$ GABAA receptors

**Authors:** \*A. KOVACEVIC<sup>1</sup>, J. B. ĐOKOVIC<sup>2</sup>, A. Z. JOVANOVIĆ<sup>3</sup>, I. R. JANCIC<sup>4</sup>, M. M. MARKOVIC<sup>5</sup>, I. A. GUNJIC<sup>5</sup>, M. M. SAVIC<sup>3</sup>;

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**Abstract:** GABA<sub>A</sub> receptors containing  $\alpha 5$  subunit ( $\alpha 5$ GABAAAR) are likely involved in inflammation-related behavioral changes, but their pharmacological manipulation in corresponding models yielded ambiguous results. Here, we examined behavioral effects of GL-II-73, an  $\alpha 5$ GABAAAR-preferring positive allosteric modulator (PAM), and GABRA5 mRNA expression in lipopolysaccharide (LPS)-induced model of sickness and anhedonia. Male and female 3-month old C57BL/6 mice (N=85), previously habituated to 1% sucrose consumption, received 5 single daily intraperitoneal (i.p.) injections of GL-II-73 dosed at 10 mg/kg and/or vehicle (SOL). Treatments were administered -48 h, -24 h, 0 h (pre-LPS) and 24 h and 48 h post-LPS i.p. injection (0.5 mg/kg) in the following manner: Group I (control): SOL pre- and post-LPS; II (prophylactic, P): GL-II-73 pre-LPS, SOL post-LPS; III (therapeutic, T): SOL pre-LPS, GL-II-73 post-LPS; IV (combined P+T, PT): GL-II-73 pre- and post-LPS. Body weight (BW) change, food and liquid intake (FI, LI), distance travelled during 5 min (D) of open field test (measures of sickness), sucrose preference (SP) during a 4-hour sucrose preference test (SPT) (correlate of anhedonia at 48 h) and liquid intake during SPT (LISPT) were assessed daily both pre- and post-LPS. At the end of behavioral testing, the prefrontal cortex (PFC) was isolated for RT-qPCR to assess relative GABRA5 and IL1B gene expression with GAPDH as housekeeping gene. Data were analyzed by two- or three-way ANOVA with (behavioral data) or without (PCR data) repeated measures, followed by Bonferroni *post hoc* tests. During habituation and pre-LPS phase, males had higher LI and LISPT and reached plateau SP earlier. As expected, LPS reduced all behavioral parameters, but sickness was more pronounced at 24 h and in males, with the exception of LI, which recovered by 48 h and remained higher in males. Pre-LPS treatment with GL-II-73 increased D compared to SOL. Neither P, T or PT exposure to GL-II-73 affected LPS-induced anhedonia. Sickness might be slightly more pronounced after PT than after P for LI, FI, dBW and D, particularly in females ( $p < 0.10$ ). GABRA5 mRNA expression was significantly decreased in recovered females compared to anhedonic females and recovered males. In general, male mice showed more pronounced sickness than female mice after LPS exposure. GL-II-73,  $\alpha 5$ GABAAAR PAM, did not prevent or exacerbate LPS-induced anhedonia, but may have slightly affected sickness. The increased GABRA5 mRNA expression in males and anhedonic females confirms the involvement of  $\alpha 5$ GABAAAR in sex-dependent inflammatory pathways underlying anhedonia.

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Science Fund of the Republic of Serbia, Grant No. 7749108., This research was supported by the Ministry of Education, Science and Technological Development, Republic of Serbia; grant agreement: No. 451-03-47/2023-01/200161.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); M.M.S. is listed inventor on patent covering the synthesis and use of the compound..

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.02/E10

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** R01MH084894

**Title:** Psychedelic regulation of hippocampal cytokines and behavior in an acute LPS-induced neuroinflammation model

**Authors:** \*M. FIORILLO, J. GONZÁLEZ-MAESO;  
Dept. of Physiol. and Biophysics, Virginia Commonwealth Univ., Richmond, VA

**Abstract:** Psychedelics have emerged as promising therapeutics for psychiatric disorders like depression and anxiety, with recent evidence suggesting anti-inflammatory properties. However, the mechanisms underlying their immunomodulatory actions in the brain remain poorly understood. Investigating how psychedelics influence neuroimmune pathways could provide valuable insights into serotonergic neuroprotection and inform novel therapeutic strategies for diseases driven by neuroinflammation. This study examined the effects of serotonin 2A receptor (5-HT<sub>2A</sub>R) agonist DOI ((±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride) on hippocampal cytokine expression, body weight changes, and inflammation-associated behavioral alterations in a lipopolysaccharide (LPS)-induced neuroinflammation model. Male C57BL/6J mice, aged 8-10 weeks, received intraperitoneal (i.p.) injection of DOI at varying doses, with hippocampal cytokines analyzed 24h post-injection to assess dose-dependent effects. In a separate cohort, DOI pre-treatment was administered 24h before LPS (*E. Coli* O55:B5, 1 mg/kg, i.p.), with hippocampi collected 4h post-LPS. Cytokine levels (IL-2, IL-4, IL-6, IL-10, IL-13, TNF- $\alpha$ ) were quantified using the BioLegend LEGENDplex multiplex assay. Body weight was monitored to evaluate DOI's effect against LPS-induced weight loss, and behavioral responses assessed 24h post-LPS using the open field test (OFT) and forced swim test (FST) to measure locomotor activity and depressive-like behavior, respectively. Results showed that DOI modulates immune responses following systemic inflammatory challenge, mitigating LPS-induced pro-inflammatory cytokines in the hippocampus and weight loss. Ongoing analyses are examining the impact of DOI on hippocampal cytokines in the absence of LPS, as well as LPS-induced behavioral alterations in the OFT and FST. Overall, our study shows that DOI modulates neuroinflammatory effects of acute systemic peripheral immune challenge by altering cytokine profiles. These findings

indicate that psychedelics may have therapeutic potential in treating conditions characterized by neuroinflammation, such as neurodegenerative disorders.

**Disclosures:** M. Fiorillo: None. J. González-Maeso: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.03/E11

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Ceftriaxone-driven disruptions to the gut microbiome modulate neurobehavioral processes, neuroinflammation, and neuroplasticity

**Authors:** \*O. KOKA<sup>1</sup>, D. M. FRANCESCUTTI<sup>1</sup>, D. CHAUDHARI<sup>1</sup>, K. SAL<sup>2</sup>, A. D. WINTERS<sup>1</sup>, M. ANGOA-PEREZ<sup>1</sup>;

<sup>1</sup>Wayne State Univ. Sch. of Med., Detroit, MI; <sup>2</sup>Cornerstone Univ., Grand Rapids, MI

**Abstract:** Introduction: The gut-brain axis is a bidirectional communication pathway in which gut microbiota can influence neurobiological and behavioral output. Recent studies have shown that antibiotics, while essential for combating bacterial infections, exert profound off-target effects on host physiology through the disruption of the gut microbiome. The purpose of this study was to observe the neurobehavioral and neuroinflammatory effects of ceftriaxone (CTX) in mice.

Methodology: Male C57BL/6 mice were administered CTX via oral gavage once per day for 4 consecutive days, while controls were administered sterile water. Fecal samples were collected on days 1, 2, and 5 for bacterial load and gut microbiome analysis. Mice were subject to behavioral testing after 4 days of CTX treatment. Tissue from the striatum, hippocampus, frontal cortex, and colon was collected and used for immunoblotting.

Results: Behavioral testing revealed that after 4 days of CTX treatment, mice exhibited significantly impaired memory (novel object recognition). In addition, CTX-treated mice displayed significantly decreased sensitivity to pain (thermal plantar test). Bacterial load was significantly reduced after 1 day of CTX treatment and remained reduced until day 5. Gut microbiome analysis showed a significant decrease in richness, evenness, and heterogeneity after CTX treatment, as well as a significant disruption in microbial structure. GPR109 expression in CTX-treated mice was slightly decreased in striatal tissue. PSD95 expression was shown to be increased in hippocampal tissue of CTX-treated mice. In addition, Calprotectin in colon samples were elevated in mice receiving CTX treatment.

Conclusion: Short-term ceftriaxone treatment disrupts gut microbial composition and diversity, resulting in measurable changes in behavior and inflammatory signaling. CTX-induced impairments in memory and reduced pain sensitivity were accompanied by decreased striatal expression of GPR109, a receptor integral to gut-brain axis communication. Elevated PSD95 expression in the hippocampus suggests altered synaptic signaling in a region critical for

memory processing. Increased colonic calprotectin levels confirm intestinal inflammation as a consequence of CTX treatment, further implicating gut dysbiosis in the modulation of neuroimmune pathways. This study highlights the modulatory role of the gut microbiome in maintaining neural function and suggests that even brief antibiotic exposure may influence behavior, inflammation, and neuroplasticity through microbiome-mediated pathways.

**Disclosures:** O. koka: None. D.M. Francescutti: None. D. Chaudhari: None. K. Sal: None. A.D. Winters: None. M. Angoa-Perez: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.04/E12

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH R21AT011238  
WVU Synergy Grant  
NIH P20-GM103434  
NIH U54-GM104942  
NIH R21-ES034942

**Title:** Combined effects of dim light at night and burn pit emission inhalation exposure on neuroinflammatory and behavioral outcomes in mice

**Authors:** \*P. SHARMA<sup>1</sup>, V. SETOLA<sup>1</sup>, J. C. WALTON<sup>1</sup>, A. RANPARA<sup>2</sup>, W. T. GOLDSMITH<sup>2</sup>, T. NURKIEWICZ<sup>2</sup>, R. J. NELSON<sup>1</sup>;  
<sup>1</sup>Dept. of Neurosci., <sup>2</sup>Dept. of Physiology, Pharmacol. & Toxicology, West Virginia Univ., Morgantown, WV

**Abstract:** The increasing global exposure to artificial light at night and air pollution presents an emerging environmental health concern. Although both of these factors have been independently associated with adverse health outcomes, their combined neurological and neurobehavioral effects remain largely unspecified. Urban air pollution continues to rise due to factors such as high population density, expanding industrial activities, and increasing transportation demands, while military burn pits are used widely in combat zones for waste disposal. This study aimed to investigate the interaction between dim light at night (DLAN) and burn pit toxins (BPT) exposure on neuroinflammatory, neurochemical, and behavioral outcomes in mice. Male Swiss Webster mice (~2 months old) were used for this study. Mice were assigned to one of four experimental groups (n= 8/group): (1) LD-FA (standard light-dark cycle + filtered air), (2) LD-BPT (standard light-dark cycle + burn pit exposure), (3) DLAN-FA (dim light at night + filtered air), and (4) DLAN-BPT (dim light at night + burn pit exposure). Mice were housed in either standard light-dark (150:0 lux; 14:10 h) or DLAN (150:5 lux; 14:10 h) conditions for four weeks. Subsequently, mice were given a single exposure to either filtered air or burn pit combustion

emissions (a mixture of 80% wood, 10% rubber, 10% plastic, and jet fuel) for 4 h in a whole-body inhalation exposure chamber. The aerosol mass concentration during the exposure was 6.90 mg/m<sup>3</sup> and the particle count concentration was 4.03 E<sup>6</sup>/#cc. This exposure paradigm produced a deposited dose of 5.37 µg/mouse. Twenty-four hours post-exposure, mice were assessed in an Open Field Test (OFT), Elevated Plus Maze (EPM), and Y-maze, prior to being euthanized for sample collection. Neither dLAN nor BPT affected anxiety-like behavior (EPM, central tendency in OFT) or working memory (Y-maze) 24 hr after BPT exposure. However, BPT exposure, independent of lighting condition, significantly decreased open field measures ( $p < 0.05$ ); including total locomotor activity, velocity, and rearing. Post-hoc pairwise comparisons suggest that mice under standard light-dark conditions were more behaviorally sensitive to acute burn pit exposure than those exposed to DLAN. Ongoing analyses include the quantification of monoamine neurotransmitters (dopamine, serotonin and norepinephrine) using HPLC-ECD in one hemisphere of the brain (cortex, hippocampus, striatum) and qRT-PCR for inflammatory markers (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-10) in the other. The results of histological examination of lung tissues will also be presented.

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## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.05/E13

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Inflammation, Electromyographic, Behavioral, and Histological Characterization of TREX1<sup>-/-</sup> mice: Physiological Consequences of Chronic Inflammation

**Authors:** \*Y. TUFAIL<sup>1</sup>, K. W. FEJGIN<sup>2</sup>, C. PEDERSEN<sup>2</sup>, B. J. HALL<sup>3</sup>;

<sup>1</sup>Lundbeck La Jolla Res. Ctr., San Diego, CA; <sup>2</sup>H. Lundbeck A/S, Copenhagen, Denmark;

<sup>3</sup>Circuit Biol., H Lundbeck, Valby, Denmark

**Abstract:** Three prime repair exonuclease 1 (TREX1), the most abundant mammalian DNA-specific exonuclease, plays a critical role in degrading cytosolic DNA to prevent its aberrant accumulation and maintain innate immune tolerance. Pathogenic mutations in TREX1 are associated with severe autoimmune disorders, including Aicardi-Goutières syndrome (AGS), systemic lupus erythematosus, and chilblain lupus. Both published literature and our internal data demonstrate pronounced type I interferon (IFN) upregulation and muscle inflammation in the TREX1 deficient (TREX1<sup>-/-</sup>) mouse model, mirroring core pathological features of idiopathic inflammatory myopathies (IIMs), especially dermatomyositis (DM). Critically, these inflammatory responses often impact the peripheral nervous system, contributing to neuroinflammation. While muscle weakness and electromyographic (EMG) abnormalities are characteristic of IIM, functional neuromuscular deficits have not been previously described in

the TREX1<sup>-/-</sup> model. Here, we are the first to show that TREX1<sup>-/-</sup> mice exhibit significantly reduced compound muscle action potential (CMAP) amplitudes and waveform abnormalities, consistent with IIM patients. Additionally, TREX1<sup>-/-</sup> mice have weaker hindlimb grip strength and commit more foot slips while taking longer to traverse a stationary beam. Taken together, these EMG and behavioral data provide evidence extending the molecular and histological abnormalities of neuromuscular dysfunction observed in the TREX1 mouse model and support its use as a disease-relevant model for IIM, suitable for testing of potential therapeutics.

**Disclosures:** Y. Tufail: None. K.W. Fejgin: None. C. Pedersen: None. B.J. Hall: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.06/Web Only

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Volumetric brain alterations associated with a high-fat, high-fructose obesogenic diet: insights from cross-sectional and longitudinal MRI in mice

**Authors:** \*C. ZHAN<sup>1</sup>, L. JIANG<sup>2</sup>, S. ELSAID<sup>2</sup>, X. LI<sup>2</sup>, S. XU<sup>2</sup>, S. TEE<sup>2</sup>;

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**Abstract:** Non-Alcoholic Fatty Liver Disease (NAFLD) is a major consequence of obesity in humans, with effects that extend beyond the liver to other vital organs, including the brain. While longitudinal studies in humans have suggested associations between NAFLD and changes to the brain, the direct impact of its more advanced form, non-alcoholic steatohepatitis (NASH), on brain development remains poorly understood. To investigate this association, we used a mouse model to examine how NASH influences brain structure over time. We studied 20 male C57BL/6NTac mice fed a high-fat, high-fructose (HFHF) obesogenic diet to induce NASH, alongside 15 control mice maintained on a standard chow diet, beginning at 6 weeks of age. All animals underwent T2-weighted MRI brain scans at 14 weeks (baseline) and six months later, at 38 weeks. We conducted region-of-interest (ROI)-based volumetric analyses to assess brain changes cross-sectionally and over time. At baseline, NASH mice exhibit significant reductions in whole brain volume, particularly in the posterior hippocampus, compared to controls. Six months later, despite a partial volumetric increase, ROI analysis shows persistent volume loss in the posterior dorsal hippocampus, while the posterior neocortex shows compensatory hypertrophy. Longitudinally, control mice maintain stable brain volumes with age-typical patterns, including hippocampal increases (notably in total and anterior-dorsal regions) and neocortical decreases (notably in middle and posterior regions). NASH mice show compensatory brain growth with regional patterns similar to controls, but this apparent recovery likely reflects chronic neuroinflammatory responses, such as microglial activation, astrocytic hypertrophy, and edema, rather than true tissue restoration. Our findings indicate that early exposure to an HFHF

diet induces brain atrophy in memory- and sensory-related regions during the juvenile period, followed by partial recovery and a biphasic response driven by inflammation-associated volume expansion. Crucially, the persistent reduction in posterior hippocampal volume suggests lasting structural vulnerability despite compensatory growth elsewhere in the brain. These region-specific changes highlight complex interactions between normal developmental trajectories and NASH-related pathology. This study underscores the importance of early dietary interventions to mitigate long-term neuroanatomical consequences of metabolic dysfunction. The results show the developing brain is particularly vulnerable to early-life metabolic stress, with impacts that persist into young adulthood despite apparent recovery.

**Disclosures:** C. Zhan: None. L. Jiang: None. S. Elsaid: None. X. Li: None. S. Xu: None. S. Tee: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.07/E14

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant EY029795  
NIH Grant EY030077  
CRI Grant 221708

**Title:** S100a9: a key neuroinflammatory mediator for neurodegenerative and microvascular changes in the retina

**Authors:** \*S. GO<sup>1</sup>, U. ADDI<sup>1</sup>, S. SOKUPA<sup>1</sup>, T. CONNOR<sup>2</sup>, Y. G. GOMEZ<sup>1</sup>, S. CHAURASIA<sup>3</sup>; <sup>2</sup>Dept. of Ophthalmology and Visual Sci., <sup>3</sup>Dept. of Cell Biology, Neurobio. and Anat., <sup>1</sup>Med. Col. of Wisconsin, Milwaukee, WI

**Abstract:** Inflammatory pathways play a critical role in the progression of diabetic retinopathy (DR) due to their links to neurodegenerative and microvascular damage. Our preliminary studies suggest that S100A9, an endogenous myeloid-related damage-associated molecular patterns (DAMPs) protein, was highly associated with the severity of DR in type 2 diabetes (T2D) patients. The present study was designed to determine the role of S100A9 in the retina. We used 8 to 10-week-old C57BL/6J WT mice, which received either 25  $\mu$ M of recombinant mouse S100A9 (rmS100A9), 50  $\mu$ M rmS100A9, or BSS via intravitreal injections, and a naïve group with no injections. All groups were clinically imaged for 2 weeks post-injections, fundus and fluorescein angiography (FFA) images, optical coherence tomography (OCT), and electroretinogram (ERG) for retinal function. Whole retinal flat mount and trypsin digest were performed to assess structural integrity and microvascular damage in the retina. Two weeks after injection mice injected with rmS100A9 displayed severe retinal atrophy and microvascular damage in fundus, FFA, and OCT images compared to the naïve or BSS group. Mice injected



with 25  $\mu$ M and 50  $\mu$ M of rmS100A9 had attenuated ERG a-wave and b-wave amplitudes, displaying retinal dysfunction in their photoreceptors and bipolar cells. The intravitreal injection of rmS100A9 demonstrated neurodegenerative and microvascular abnormalities, indicating its significant neuroinflammatory role in the retina.

**Disclosures:** S. Go: None. U. Addi: None. S. Sokupa: None. T. Connor: None. Y.G. Gomez: None. S. Chaurasia: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.08/E15

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Department of Defense grant W81XWH-16-1-0586 to NMF

**Title:** Amelioration of multiple neurochemical perturbations by the neoglycoconjugate LNFPIII in a pesticide-nerve agent prophylactic preclinical model of Gulf War Illness: effects of sex

**Authors:** \*B. HUDSON, T. KALINOWSKI, F. TEJEDOR ROJAS, J. J. WAGNER, N. M. FILIPOV;  
Physiol. and Pharmacol., Univ. of Georgia, Athens, GA

**Abstract:** Gulf War Illness (GWI) is a multisymptomatic illness related to concomitant exposure to multiple toxicants, including permethrin (PM) and pyridostigmine bromide (PB) during the 1990-1991 Gulf War. 30% of Gulf War veterans have since been diagnosed with GWI, with limited therapeutic options. Notably, this conflict was the first to see female US service members on the frontline. There is a paucity of research investigating sex differences in both neurophysiological underpinnings and efficacy of therapeutics in a GWI context. To address this research gap, we investigated long-term effects of GWI chemical exposure on neurochemistry and synaptic physiology using an established preclinical GWI model, which consisted of 10-day intraperitoneal treatment of 8-9-week-old male and female C57BL6 mice with PB (0.7 mg/kg) and PM (200 mg/kg). 9 months post-exposure, subsets of both control and GWI mice were treated with a novel immunotherapeutic, Lacto-N-Fucopentaose-III (LNFPIII, 35ug, twice a week) for 3 months prior to neurochemistry analysis with HPLC-ECD. Levels of (1) dopamine (DA) and its metabolites DOPAC, 3-MT, and HVA, (2) serotonin (5-HT) and its metabolite 5-HIAA, (3) norepinephrine (NE) and its metabolite MHPG, and (4) the amino acid neurotransmitters GABA, glutamate, and glutamine were measured in micropunches taken from the prefrontal cortex, striatum, hippocampus, brainstem, and cerebellum. Analyses up to date indicate sex-specific monoamine alterations in the prefrontal cortex, where GWI treatment increased MHPG in females and decreased 5-HIAA and MHPG in males. These effects were ameliorated with delayed LNFPIII intervention in males. Striatal DOPAC and cerebellar 5-HIAA were decreased in GWI males, whereas striatal DA and 5-HT levels were increased. In the

brainstem, both GWI males and females had increased MHPG, while only GWI males had increased 5-HT and 5-HIAA. These data suggest persistent and sex-specific neurochemical alterations related to GWI chemical exposure, which may underlie neurologic symptoms of the disease. Monoamine imbalance in the prefrontal cortex suggests sex-independent cognitive dysfunction that may manifest differently given that GWI females showed noradrenergic alterations, while GWI males had noradrenergic and serotonergic alterations. Striatal and cerebellar results suggest a male bias of GWI motor symptoms. Delayed LNFPIII treatment restored monoamine homeostasis in the prefrontal cortex of males, highlighting its potential as a GWI therapeutic. These data highlight the need for considering sex as a factor in GWI, particularly in the context of evaluating treatment efficacy and disease endophenotypes.

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## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.09/E16

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Pharmacological reversal of LPS-induced cognitive impairments: evidence for inflammation-dependent and independent mechanisms

**Authors:** E. ANDRIAMBELOSON, C. DUCHEMIN, L. PETER, C. PINAULT, A. KIENTZI, F. LAUGA, E. POIRAUD, B. HUYARD, \*S. WAGNER;  
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**Abstract:** Chronic, low grade peripheral inflammation—such as that arising from gut microbiota dysbiosis—has emerged as a critical driver of neuroinflammatory processes and cognitive decline in neurodegenerative disorders (e.g., Alzheimer’s disease, Parkinson’s disease). Lipopolysaccharide (LPS) administration in rodents models this connection by inducing systemic inflammation that penetrates the blood-brain barrier, activates microglia, and impairs synaptic function and memory. A comprehensive preclinical evaluation of candidate therapeutics across diverse mechanisms is essential to identify strategies that counteract inflammation-mediated cognitive deficits. The present study assessed the efficacy of 17 pharmacological agents—spanning anti-inflammatory, antioxidant, synaptic modulatory, metabolic, and neurotrophic mechanisms—in preventing or reversing LPS-induced cognitive impairments in CD-1 mice. To this end, CD-1 mice received a single intraperitoneal (i.p.) injection of LPS (0.25 mg/kg). This non-septic dose induced a persistent cognitive deficit lasting three weeks. Cognitive performance was evaluated using the spontaneous alternation task in the T maze, with LPS-treated mice showing a significant reduction in alternation percentage compared to vehicle-treated controls. Fifteen compounds proved effective in reversing cognitive deficits and were categorized as follows: i) Anti-inflammatory NSAIDs & Steroids: Ibuprofen, indomethacin, sulindac,

dexamethasone. ii) Antioxidants & Autophagy Modulators: Resveratrol, N-acetylcysteine, spermidine, docosahexaenoic acid, cinnamaldehyde. iii) Synaptic & Neurotransmitter Modulators: Memantine, donepezil, GRN 529. iv) Metabolic & Signaling Agents: Metformin, semaglutide, neflamapimod. Two interventions—nilotinib and methylene blue—were ineffective. This broad-spectrum evaluation demonstrates that targeting peripheral inflammation and its central sequelae via multiple pharmacological modalities can reverse LPS-induced cognitive deficits. Remarkably, synaptic and neurotransmitter modulators improved cognition independently of anti-inflammatory effects, suggesting that direct restoration of synaptic function can bypass inflammatory cascades. The convergence of benefits across anti-inflammation, oxidative stress reduction, synaptic modulation, and metabolic regulation underscores the multifactorial nature of inflammation-driven neurodegeneration. Identifying both effective and ineffective agents highlights the model's translational potential and discriminative validity.

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## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.10/E17

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Oral MCT supplementation reduces anxiety-like behavior and modulates BDNF response in a PTSD rodent model

**Authors:** \*D. YOSHIOKA<sup>1</sup>, T. YAMANASHI<sup>2</sup>, K. KOMATSU<sup>3</sup>, N. KAJITANI<sup>4</sup>, C. USHIDA<sup>5</sup>, M. NAKAMOTO<sup>2</sup>, M. IWATA<sup>6</sup>;

<sup>1</sup>Tottori Univ. Sch. of Med., Yonago/ Tottori, Japan; <sup>2</sup>Tottori Univ., Yonago, Japan; <sup>3</sup>Tottori Univ., Yonago-shi/Tottori-ken, Japan; <sup>4</sup>Division of Neuropsychiatry, Tottori Univ., Yonago-shi, Japan; <sup>5</sup>Tottori Univ., Yonago / Tottori, Japan; <sup>6</sup>Tottori Univ., Yonago, Tottori, Japan

**Abstract:** Post-traumatic stress disorder (PTSD) is a debilitating psychiatric condition that occurs after severe trauma, such as war or interpersonal violence. Neuroinflammation and reduced brain-derived neurotrophic factor (BDNF) levels are thought to play a central role in PTSD pathophysiology. We previously showed that subcutaneous administration of  $\beta$ -hydroxybutyrate (BHB), a ketone body, attenuates PTSD-like anxiety behaviors and suppresses inflammatory cytokines in a rat model using the single prolonged stress (SPS) paradigm (Yamanashi et al. 2020 Sci Rep). However, the invasive nature of this administration method limits its translational applicability. Medium-chain triglycerides (MCTs) are dietary lipids rapidly converted into BHB in the liver and are a practical alternative to direct BHB injection. In this study, we evaluated whether oral MCT oil supplementation could alleviate PTSD-like

behaviors and modulate stress-induced molecular responses. Six-week-old male Sprague-Dawley rats were exposed to SPS and then administered either MCT or long-chain triglyceride (LCT) oil (control) daily via oral gavage for 14 days. Anxiety-like behavior was assessed using the elevated plus maze (EPM) and open field test (OFT). MCT-treated rats showed reduced anxiety index scores in the EPM compared to LCT-treated controls ( $p = 0.036$ ). To investigate underlying mechanisms, we assessed serum and brain levels of inflammatory cytokines and BDNF under both resting and acute stress conditions. Acute stress was induced by applying a 1-hour restraint immediately prior to euthanasia, allowing us to examine rapid stress-related molecular responses. Under this condition, serum BDNF levels were significantly elevated in SPS-exposed rats receiving LCT, indicating that SPS enhanced BDNF responsiveness to acute stress. Importantly, this elevation was significantly blunted in the MCT-treated group ( $p = 0.0019$ ), suggesting that MCT supplementation suppressed the exaggerated BDNF response to acute stress observed in SPS rats. No significant differences were observed in serum or brain cytokines between the groups. These findings suggest that oral MCT oil mitigates PTSD-like anxiety behaviors and attenuates the acute stress-induced increase in BDNF reactivity following trauma exposure. This non-invasive intervention may provide a novel metabolic approach for the treatment or prevention of PTSD. All procedures were conducted in accordance with the ethical guidelines of the Tottori University Animal Care and Use Committee and complied with institutional regulations.

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## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.11/E18

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** R01DE029074

**Title:** Srebp1c-dependent lipid modification in the insular cortex regulates chronic overlapping pain

**Authors:** \*M. H. SHAHED<sup>1</sup>, H. MEKONEN<sup>1</sup>, M. L. KEASER<sup>1</sup>, J. T. DA SILVA<sup>1</sup>, O. K. MELEMEDJIAN<sup>1</sup>, D. A. SEMINOWICZ<sup>2</sup>, R. J. TRAUB<sup>1</sup>;

<sup>1</sup>Neural and Pain Sci., Univ. of Maryland Sch. of Dent., Baltimore, MD; <sup>2</sup>Med. Biophysics, Univ. of Maryland, Baltimore, London, ON, Canada

**Abstract:** Chronic pain, impacting 21% of adults in the U.S., remains a critical medical challenge with few effective therapies. Chronic overlapping pain conditions (COPCs), such as temporomandibular disorder (TMD), irritable bowel syndrome (IBS), and fibromyalgia, frequently co-occur, predominantly affect women, and are often worsened by stress. While

peripheral mechanisms may underlie individual pain conditions, central nervous system dysregulation appears to play a key role in COPCs. Current therapies are insufficient, highlighting the need to target CNS pathways for effective intervention. This study seeks to identify novel, non-addictive pharmacological targets to alleviate COPC-associated pain using a rat model of comorbid pain hypersensitivity (CPH), in which orofacial pain and stress lead to chronic visceral hypersensitivity. We investigated brain activity and connectivity changes using fMRI and analyzed lipid and metabolite alterations by spatial lipidomics using mass spectrometry imaging (MSI) to identify molecular mechanisms underlying pain. Preliminary results revealed heightened visceral hypersensitivity in CPH rats, with fMRI indicating increased activity and disrupted connectivity in the insula cortex (IC), mPFC, and amygdala. MSI analysis revealed altered lipid profiles in the IC, particularly changes in fatty acid elongation and desaturation patterns. Since SREBP1c regulates key enzymes mediating fatty acid elongation and desaturation, such as ELOVL2, ELOVL6, and SCD, we targeted SREBP1c using siRNA in the IC. This intervention reduced referred pain by ~60%, establishing a mechanistic link between lipid metabolism and pain modulation. Our findings identify the IC and modulation of lipid populations as promising therapeutic targets for effective chronic pain intervention.

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## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.12/E19

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Effects of toluene exposure on iNOS expression and nitrosative stress in brain regions of young rats

**Authors:** \*M. M. I. F. MATA, Jr<sup>1</sup>, O. R. GALICIA, Sr.<sup>2</sup>, M. H. BUENROSTRO-JAUREGUI, Sr.<sup>3</sup>;

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**Abstract:** Toluene is a major component of solvents often inhaled by adolescents for euphoric effects, which are mediated by dopamine release and activation of the reward system. Recent studies focus on its neurotoxic effects on the mesocorticolimbic dopaminergic system, particularly via oxidative stress—an imbalance between elevated reactive oxygen species (ROS) and insufficient antioxidant defenses—resulting in neuronal damage and death. While ROS are key contributors to oxidative damage, reactive nitrogen species (RNS), such as nitric oxide (NO), also play a role under certain conditions. NO is synthesized from L-arginine by inducible nitric oxide synthase (iNOS), mainly found in glial cells like astrocytes and microglia. Though iNOS helps protect neurons from pathogens by producing NO, excessive NO leads to nitrosative stress

and neuronal injury. This study aimed to determine iNOS expression as an indicator of RNS activity in the mesocorticolimbic system of young rats exposed to toluene. Male Wistar rats (35 days old) were exposed to air or toluene at 2000 ppm for 30 minutes daily over two weeks. Afterward, the ventral and dorsal striatum, hippocampus, and prefrontal cortex were dissected, and iNOS expression was analyzed using Western blot. Results revealed a significant increase in iNOS expression in the ventral and dorsal striatum of toluene-exposed rats, indicating elevated NO production and possible nitrosative stress in these regions. However, no significant changes were observed in the hippocampus or prefrontal cortex. These findings suggest that toluene exposure induces neurochemical alterations in brain regions associated with reward and motor function, possibly through inflammatory and oxidative mechanisms. The absence of changes in other areas might reflect regional vulnerability or delayed response. Overall, the data underscore toluene's neurotoxic impact on brain health, especially concerning for adolescents, a population particularly vulnerable to long-term neurological consequences from solvent abuse.

**Disclosures:** M.M.I.F. Mata: None. O.R. Galicia: None. M.H. Buenrostro-jauregui: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.13/E20

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** American Heart Assoc. 24PRE1184797  
NIAAA 5R01AA027096  
NINDS R01NS03261

**Title:** Effects of Tlr3-dependent innate immune activation and chronic alcohol consumption on gene expression in brain micro-vessels and Blood Brain Barrier permeability

**Authors:** \*B. R. KISBY<sup>1</sup>, C. BUSTAMANTE<sup>2</sup>, S. SHANMUGAM<sup>2</sup>, O. PONOMAREVA<sup>2</sup>, I. CASTRO-PIEDRAS<sup>3</sup>, I. PONOMAREV<sup>2</sup>;

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**Abstract:** Chronic high alcohol (ethanol) drinking is one of the characteristics of Alcohol Use Disorder (AUD). Toll-like receptor 3 (Tlr3) - dependent innate immune activation in rodents contributes to escalated ethanol consumption in a sex and genotype-dependent manner and our preliminary data suggest that these effects may be mediated by Tlr3 activation in microvasculature cell types, including endothelial cells (ECs). We hypothesize that Tlr3 activation-induced changes in gene expression in these cell types contribute to blood brain barrier (BBB) dysfunction and escalated alcohol intake. The goal of this study was to determine the effects of Tlr3 activation and/or chronic alcohol drinking on gene expression in enriched brain microvasculature and BBB permeability in high-drinking FVB/NJ X C57BL/6J F1 hybrid

mice. Animals were randomly assigned to receive repeated injections of Poly(I:C) (PIC), a Tlr3 agonist, or saline (9 injections total). Mice were allowed to choose between alcohol or water every other day (18 drinking sessions) and were assigned to one of four groups: saline/water (SW), saline/ethanol (SE), PIC/water (PW), and PIC/ethanol (PE). Brains were harvested 24 hours after the final alcohol session, micro-vessels from frontal cortex were purified using mechanical homogenization and density-gradient centrifugation, and RNA sequencing was performed to compare gene expression between groups. To assess BBB permeability and vascular morphology, a separate cohort of mice were administered fluorescently labeled Dextran (3 and 10 kDa) and lectin (LEL) followed by intracardiac perfusion. Tlr3 activation with PIC resulted in escalated ethanol consumption in male mice and we identified 1,588 genes differentially expressed (DEGs) between PE and SE groups at nominal p-value of less than 0.05 and 74 DEGs at 5% FDR. Top up-regulated genes were *Ifitm3*, *Rsad2*, *H2-K1*, and *Ifi44*, suggesting immune response in ECs. We validated some of these results in an immortalized human EC line (hCMEC/D3) after 24-hour exposure to ethanol, PIC, or their combination exposure. Our BBB permeability results demonstrated an increased “leakiness” for both 3 and 10 kDa Dextran after PIC treatment. Morphological analysis showed altered vessel diameter composition in animals after immune activation. These findings suggest that repeated Tlr3 activation results in immune-related changes in gene expression in the vasculature, potentially contributing to decreased BBB integrity and increased ethanol consumption. Future experiments will examine the effects of Tlr3 cell-type specific knockouts in microvasculature cell types.

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## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.14/E21

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NEURO-ID BP-Endure Grant 2R25NS080687-11

**Title:** Effects of endocannabinoid system activation in neuroinflammatory induced depressive and anxiety behaviors through lipopolysaccharide injection and its role on the insular cortex

**Authors:** \*D. UMANA<sup>1</sup>, S. SANTOS<sup>2</sup>, A. CORRETTJER<sup>3</sup>, C. MALDONADO IRIZARRY<sup>4</sup>;  
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**Abstract:** Neuroinflammation has been increasingly implicated in the pathophysiology of mood disorders such as anxiety and depression. The endocannabinoid system (ECS), particularly the CB1 receptor (CB1R), plays a crucial role in emotional regulation, and its dysregulation is

associated with chronic stress and inflammatory states. This study investigates whether the use of URB 597, a fatty acid amide hydrolase (FAAH) inhibitor that increases anandamide (AEA) levels, can attenuate anxiety- and depressive-like behavior and restore CB1R protein expression in a neuroinflammation rat model. Researchers administered lipopolysaccharides (LPS) (500 µg/kg, i.p.) to male and female rats to induce mild inflammatory stress, followed by treatment with URB597 (0.1 mg/kg, i.p.). Behavioral outcomes were assessed using the Forced Swim Test (FST) and Elevated Plus Maze (EPM), while CB1R expression was measured in the anterior insular cortex (AIC) via Western blot. The group LPS/VEH spent the most time in immobility compared to the other treatment groups. Meanwhile, the treatment group URB597/LPS demonstrated significantly decreased depression-like behaviors as indicated by increased swimming and reduced immobility in FST compared to the control group. However, the EPM results showed no significant differences between the treatment groups. Molecular analysis done in the AIC revealed a substantial increase in CB1R protein expression in the URB597/LPS group compared to the LPS group. These findings suggest that increasing AEA via URB597 inhibition may reverse neuroinflammation CB1R downregulation in the AIC, a brain region responsible for emotional processing. Our data support the therapeutic potential of ECS modulation in mood disorders and highlight the AIC as a promising but underexplored target for cannabinoid-based interventions.

**Disclosures:** D. Umana: None. S. Santos: None. A. Corretjer: None. C. Maldonado Irizarry: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.15/E22

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** UNAM-DGAPA-PAPIIT Grant IN205925  
Secretaría de Ciencias, Humanidades, Tecnología e Innovación  
(SECIHTI) Grant CBF2023-2024-1431

**Title:** Lipocalin-2 participates in neuroinflammation and pain during orthodontic tooth movement in mice with type 2 diabetes

**Authors:** \*J. GARCÍA<sup>1</sup>, I. O. PEREZ-MARTINEZ<sup>2</sup>, S. CIFUENTES-MENDIOLA<sup>3</sup>, A. GARCIA-HERNANDEZ<sup>3</sup>;

<sup>1</sup>Facultad de Estudios Superiores Iztacala, UNAM, México, Mexico; <sup>2</sup>Lab. of Neurobio. of Oral Sensations, Facultad de Estudios Superiores Iztacala, UNAM, Cuautitlán México, Mexico; <sup>3</sup>Lab. of Osteoimmunology and Oral Immunol., Facultad de Estudios Superiores Iztacala, UNAM, Cuautitlán, México, Mexico



**Abstract: Introduction:** Orthodontic tooth movement (OTM) is a biomechanical process that involves the application of controlled forces to the teeth, resulting in their displacement within the alveolar bone; mediated by an interplay of cellular signaling pathways and inflammatory responses (Kraus et al. 2018). Type 2 Diabetes Mellitus (T2D) is characterized by chronic hyperglycemia and exacerbated inflammatory responses (Sanz et al. 2018), resulting in an excessive inflammation, increased pain perception, and contribute to the development of neuropathic pain (Kumar et al. 2019). Lipocalin-2 (LCN2) is a multifunctional glycoprotein, that has been proposed as a critical factor in the development and progression of diabetic neuropathy (Roman-Pintos et al., 2016), which plays a significant role in the pathogenesis of acute inflammatory pain, nociceptive pain, and the development of chronic neuropathic pain. For this reason, we aimed to investigate the effects of LCN2 inhibition in diabetic mice undergoing OTM. **Materials and Methods:** We utilized 36 four-week-old C57BL/6 male mice, divided into six groups n=6: (1) Intact, (2) OTM+ Isotype, (3) OTM+anti-LCN2, (4) T2D, (5) T2D+OTM+Isotype, and (6) T2D+OTM+anti-LCN2. Diabetic groups were induced by a high-fat diet, followed by intraperitoneal injection of streptozotocin. Mice undergoing OTM received an orthodontic appliance, inducing tooth displacement of the first molar for 3 days. Mice with LCN2 function inhibition received administration of an anti-LCN2 antibody. To analyze facial expressions indicative of pain, we developed visual machine learning algorithms. To assess neuroinflammation, we performed immunofluorescence staining for NFkB, TNF-alpha, Iba-1, and LCN2 in the anterior cingulate cortex (ACC). **Results:** Analysis of OTM revealed that the OTM+anti-LCN2 group exhibited reduced OTM compared to the OTM+Isotype group ( $p=0.0395$ ). T2D+OTM+anti-LCN2 group also showed decreased OTM relative to the T2D+OTM+Isotype group ( $p=0.0002$ ). Facial expression analysis indicated that OTM+Isotype and T2D+OTM+Isotype groups demonstrated a greater similarity to the pain prototype compared to Intact and T2D groups respectively ( $p=0.0012$ ,  $p<0.0001$ ); OTM+anti-LCN2 and T2D+OTM+anti-LCN2 groups did not show significant differences from Intact and T2D groups respectively ( $p=0.9837$ ,  $p=0.0528$ ). These findings suggest that the anti-LCN2 antibody effectively reduces the similarity of facial expressions to the pain prototype in T2D mice undergoing OTM. T2D+OTM+Isotype group showed increased activation of microglia compared to all groups ( $p<0.05$ ). T2D+OTM+antiLCN2 showed a decrease in activation of microglia

**Disclosures:** J. García: None. I.O. Perez-Martinez: None. S. Cifuentes-Mendiola: None. A. Garcia-Hernandez: None.

## Poster

### PSTR213: Neuroinflammation in Animal Models

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.16/E23

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Chronic exposure to microplastics affects the dendritic cytoarchitecture and neuroinflammation in the dentate gyrus of middle-aged mice.

**Authors:** \*T.-Y. HE<sup>1</sup>, L.-J. LEE<sup>2</sup>;

<sup>1</sup>Natl. Taiwan Univ., Taipei, Taiwan; <sup>2</sup>Anat. and Cell Biol., Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan

**Abstract:** With the increasing demand for plastic products, global plastic pollution has escalated rapidly in recent years. Microplastics (MPs), derived from the degradation of plastic waste, have become ubiquitous contaminants in water, air, soil, and sediment, entering the human body primarily through the food chain. Plastic particles have been detected in human feces, placentas, and even blood; however, their impact on brain health remains poorly understood. This is particularly concerning for the elderly population in our aging society, who may be more vulnerable to environmental insults. In this study, 5 µm MPs were administered orally to 14-month-old male C57BL/6J mice at low (7 mg/kg) and high (15 mg/kg) doses, twice weekly for one month. To assess the structural impact on the brain, dendritic architecture and spine density of granule cells in the dentate gyrus (DG) were examined using Golgi staining. Mice exposed to both low and high concentrations of MPs showed reduced dendritic length and complexity. In the high-dose group, spine density decreased in the proximal dendritic segments (25-50 µm from the soma), although spine morphology remained unchanged. Interestingly, microglial density increased specifically in the granule cell layer of the DG in MP-exposed mice, suggesting localized neuroinflammation. However, markers of adult neurogenesis, including Ki67 and doublecortin (DCX), were unaffected by MP exposure. In conclusion, these findings indicate that chronic oral exposure to MPs can compromise the structural integrity of the hippocampus in middle-aged individuals, potentially impairing cognitive and emotional function. This highlights the need for further investigation into the neurological risks associated with environmental microplastic pollution.

**Disclosures:** T. He: None. L. Lee: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.17/E24

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** BMBF Funding, Radio-EC2

**Title:** Cannabidiol mitigates radiation effects on neuronal function and synaptic plasticity in the hippocampus

**Authors:** \*M. BALLMANN<sup>1</sup>, L. BAUER<sup>2</sup>, G. SCHNEIDER<sup>3</sup>, G. MULTHOFF<sup>2</sup>, G. RAMMES<sup>4</sup>;

<sup>1</sup>Exptl. Anesthesiol., Clin. of Anesthesiol. and Intensive care, TUM Univ. Hospital, Tech. Univ. of Munich, Munich, Germany; <sup>2</sup>Dept. of Radiation Oncology, Ctr. of Translational Cancer Research, Tech. Univ. of Munich, TUM Univ. Hosp., Munich, Germany; <sup>3</sup>Anesthesiol. and

Intensive Care, Tech. Univ. Munich, Muenchen, Germany; <sup>4</sup>Anesthesiol. and Intensive Care Med., Clin. Rechts der Isar, Munich, Germany

### **Abstract: Background:**

Radiotherapy is a widely used treatment for brain tumors, but is often associated with cognitive impairments. Historically, this was attributed to irreversible DNA damage and neuronal loss. However, recent findings suggest that radiation primarily affects active cells, indicating that the resulting cognitive decline might be reversible. Research has increasingly focused on the hippocampus, a brain region critical for learning and memory. Radiation is believed to impair hippocampal function by reducing neurogenesis and increasing neuroinflammation. Consequently, anti-inflammatory treatments have emerged as potential therapeutic strategies to prevent or mitigate radiation-induced cognitive deficits.

### **Aims:**

To investigate the impact of radiotherapy in combination with cannabidiol (CBD) and fenofibrate (FF) on neuronal function and synaptic plasticity in the hippocampus. Additionally, to assess these effects in a glioblastoma mouse model.

### **Methods:**

Ten-week-old C57BL/6 mice (wild-type and glioblastoma-bearing) were administered daily drug applications of FF, CBD or left untreated as controls over a 4-week period. Two weeks into treatment, mice received partial brain radiotherapy (PBRT) with either 16 Gy or Sham (0 Gy) directed at one hemisphere. After treatment completion, hippocampal tissue was harvested for long-term potentiation (LTP) recordings. Additional analyses included assessments of dendritic spine density and morphology, as well as microglia polarization. Both irradiated and non-irradiated hemispheres were analyzed to evaluate abscopal effects.

### **Results:**

PBRT significantly impaired LTP in the irradiated hemisphere, while the contralateral hemisphere remained unaffected. Pre-treatment with CBD preserved LTP, whereas FF had no effect. Radiation reduced dendritic spine density, an effect attenuated by CBD. Furthermore, PBRT increased pro-inflammatory (M1) microglia in untreated mice; in contrast, CBD shifted polarization toward anti-inflammatory (M2) microglia. In glioblastoma-bearing mice, LTP was inhibited in tumor-affected hemispheres even without radiation. PBRT eliminated tumors but also inhibited LTP; with CBD pre-treatment, tumor clearance was preserved, and LTP was rescued.

### **Conclusion:**

These findings suggest that PBRT impairs synaptic plasticity by promoting neuroinflammation and reducing spine density. CBD mitigates these effects, supporting its therapeutic potential, even in tumor-bearing models. Further research is required to elucidate CBD's underlying molecular mechanisms.

**Disclosures:** M. Ballmann: None. L. Bauer: None. G. Schneider: None. G. Multhoff: None. G. Rammes: None.

### **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.18/E25

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** American Heart Association 25PRE1372484

**Title:** Defining the temporal dynamics of neuroinflammation in a mouse model of intraventricular hemorrhage and post-hemorrhagic hydrocephalus

**Authors:** \*M. MICHENKOVA<sup>1</sup>, D. LIMBRICK<sup>1</sup>, M. GARCIA BONILLA<sup>2</sup>;

<sup>2</sup>Neurosurg., <sup>1</sup>Virginia Commonwealth Univ., Richmond, VA

**Abstract: Introduction:** Post-hemorrhagic hydrocephalus (PHH) is a major complication of severe intraventricular hemorrhage (IVH) in preterm infants, characterized by progressive ventriculomegaly and neuroinflammation. While immune activation is known to play a role in IVH pathology and contribute to PHH pathogenesis, the temporal dynamics of immune cell infiltration in both the central nervous system and peripheral blood remain poorly defined. In this study, we used a neonatal mouse model of IVH/PHH to systematically characterize the progression of immune cell infiltration in the brain and circulation over time, to identify critical windows for intervention. **Methods:** IVH/PHH was induced via bilateral intraventricular injection of 5uL of lysed syngeneic blood or, in control animals, an equal volume of artificial cerebrospinal fluid was injected on postnatal day 4. Blood was collected via intracardiac puncture and brain was perfused with ice-cold PBS. Cortex was isolated at days 1, 3, 7, 14, and 30 post-induction (n≈7/group/time point). Infiltration of periventricular myeloid and other immune cells was assessed via flow cytometry. Ventricular volumes were quantified with magnetic resonance (T2). **Results:** Flow cytometry revealed a distinct, time-dependent pattern of leukocyte populations in the peripheral blood following IVH/PHH. Total CD45<sup>+</sup> leukocytes increased sharply between days 1 and 3 and remained consistently high through days 14 to 30. Neutrophils (CD11b<sup>+</sup> Lys6C<sup>+</sup> Lys6G<sup>+</sup>) were most prominent within the first 1-3 days, followed by a gradual rise in monocytes (CD11b<sup>+</sup> Lys6C<sup>+</sup> LysG<sup>-</sup>), peaking at day 14. . Notably, differences in lymphocyte subsets emerged at day 14, with an increase in CD335<sup>+</sup> CD49b<sup>+</sup> NK cells (11.29% vs. 7.48% of CD45<sup>+</sup> in IVH/PHH vs. aCSF, p = 0.0370) and CD8<sup>+</sup> T cells (27.2% vs. 17.9% of CD45<sup>+</sup>; p = 0.0181). **Conclusion:** These preliminary findings demonstrate a coordinated and time-dependent immune response in the blood following intraventricular hemorrhage, suggesting defined windows for potential immunomodulatory intervention and warranting further investigation.

**Disclosures:** M. Michenkova: None. D. Limbrick: None. M. Garcia Bonilla: None.

**Poster**

**PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.19/E26

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** R01 NS114561  
R01 NS114561-03S1  
Florence Gould Foundation Research Scholarship for Discovery in Stroke  
American Heart Association Postdoctoral Fellowship - 25POST1377733

**Title:** Brain molecular alterations after systemic inflammation: a mouse model of endotoxemia to assess persistent brain changes in aged mice

**Authors:** \*P. ÁVILA-GÓMEZ<sup>1</sup>, Y. SHINGAI<sup>6</sup>, C. LIU<sup>1</sup>, K. TOMINAGA<sup>1</sup>, G. FARACO<sup>2</sup>, L. GARCIA-BONILLA<sup>2</sup>, J. ANRATHER<sup>3</sup>, F. LEE<sup>4</sup>, C. IADECOLA<sup>3,1</sup>, T. SANCHEZ<sup>5,1</sup>;  
<sup>1</sup>Pathology and Lab. Med., <sup>2</sup>Feil Family Brain and Mind Res. Inst., <sup>4</sup>Psychiatry, Pharmacol.,  
<sup>5</sup>Neuroscience, Brain and Mind Res. Inst., <sup>3</sup>Weill Cornell Med., New York, NY; <sup>6</sup>Neurosurg., Tohoku Univ., Sendai, Japan

**Abstract:** Background and Significance: Clinical studies have found an association between systemic infections (e.g. sepsis), endothelial dysfunction and cognitive impairment. Despite its prevalence (affecting up to 40% of sepsis survivors), sepsis-associated long-term cognitive decline has been a neglected area of investigation. A deeper understanding of its underlying mechanisms could uncover novel therapeutic targets to mitigate this debilitating complication. Objective: To evaluate the long-term effects of sepsis in the mouse brain one year after recovery from systemic inflammation.

Methods: Young mice (10-12w) were subjected to our recently established model of sepsis-induced cognitive dysfunction (Avila-Gomez et al. eNeuro 2024). They received a 2mg/kg dose of lipopolysaccharide (LPS) intraperitoneally (or saline) during 3 consecutive days. Mice were then housed until 53-56 weeks of age, intracardially fixed and processed for histology. Images were acquired on a Lionheart FX microscope (20×) and quantified using Gen5 software. 8-10 images were acquired from posterior brain sections (−1.8 to −2.6 mm from bregma) from 3 different mice per group, both for cortex and hippocampus. Positive area was measured by thresholding and normalized by saline. Differences were assessed using unpaired t-test in GraphPad, and the statistical significance was defined as  $p < 0.05$ .

Results: The expression of the homeostatic microglia marker P2Y12 was reduced (20% reduction) in both cortex and hippocampus ( $*p < 0.05$  and  $**p < 0.01$ , respectively). There was also an increase in fibrin/fibrinogen content in the parenchymal and perivascular region of both regions ( $*p < 0.05$ ) compared with saline mice, which suggests augmented vessel leakage following systemic inflammation. Moreover, we found decreased levels of unphosphorylated neurofilament (SMI32 immunoreactivity) both in cortex ( $**p < 0.01$ ) and hippocampus ( $**p < 0.01$ ), an alteration indicative of axonal damage and found to precede neurodegeneration in Alzheimer's disease and aging. Finally, no differences in PSD-95 levels were detected in either region.

Conclusions/Impact: Our data indicate that microglial activation, the presence of extravasated plasma proteins (i.e. fibrinogen) and axonal injury persist 1 year after sepsis. Our study provides a standardized mouse model to support future mechanistic studies of mid-term and long-term sepsis-associated cognitive dysfunction, and to help unveil novel therapeutic targets for this debilitating disease.

**Disclosures:** P. Ávila-Gómez: None. Y. Shingai: None. C. Liu: None. K. Tominaga: None. G. Faraco: None. L. Garcia-Bonilla: None. J. Anrather: None. F. Lee: None. C. Iadecola: None. T. Sanchez: None.

**Poster**

**PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.20/E27

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** CF-2023-G-289

**Title:** New methodology for the detection and quantification of neuroinflammatory biomarkers in a murine model of cerebral ischemia using optical biosensors and machine learning.

**Authors:** \*O. MONTES, Jr;

Ctr. de Investigacion en Reproduccion Animal, Univ. Autonoma De Tlaxcala, Tlaxcala, Mexico

**Abstract:** Strokes are one of the most important pathologies in public health worldwide, due to their high mortality and permanent disability rates. Cerebral ischemia is the most common type, representing 85% of all cases and affecting more than 5 million people each year. Ischemic events are characterized by a decrease in blood flow to the brain, these episodes cause neuroinflammatory processes that, if not regulated, exacerbate neuronal damage, generating greater cognitive deficits and worse prognosis in patients. For this reason, in the present study we propose the development of a new methodology that allows the specific detection of 2 proinflammatory biomarkers (IL-1 and IL-6) and 2 anti-inflammatory biomarkers (IL-4 and IL-10) in cerebrospinal fluid of rats with a global cerebral ischemia event. The detection of these ILs will be performed through the development of Optical Biosensors, as well as their quantification through artificial intelligence using Machine Learning techniques. For this purpose, young intact male rats of the Sprague-Dawley strain will be used; these individuals will be included in a global cerebral ischemia protocol by occlusion of the four blood vessels and their samples will be obtained at different postischemic times. The animals will be divided into the groups; Controls, Ischemic without treatment and Ischemic with Estradiol Benzoate treatment. Our partial results show that administration of Estradiol Benzoate 30 minutes before the ischemic event inhibits IL-6 synthesis in the acute phase (2 hours) and promotes IL-10 synthesis in the subacute ischemic phase (4 and 6 hours). The present project has been approved by the institutional bioethics committee and the use of the animals will be strictly in accordance with current national animal protection regulations, as well as their use in research. In addition, they will be under permanent veterinary supervision and the number of animals will be kept to a minimum.

**Disclosures:** O. Montes: None.

**Poster**

## **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.21/E28

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Acute ketamine and psilocybin induce behavioural and molecular antidepressant-like effects in the IFN-alpha and WKY rat models of depression

**Authors:** \*E. PASCHEN<sup>1</sup>, C. MALTBY<sup>2</sup>, J. PINTO<sup>2</sup>, M. BIANCHI<sup>2</sup>;

<sup>1</sup>Ulysses Neurosci. Ltd., Loughlinstown, Ireland; <sup>2</sup>Ulysses Neurosci. Ltd., Dublin, Ireland

**Abstract:** Depression remains a major global health challenge, with current SSRIs treatments often slow-acting and ineffective for many patients. Our study aimed to assess the acute antidepressant effects of ketamine and psilocybin in both a pharmacological and innate rat model of depression. In adult males, we employed a back-translational inflammation-induced model using chronic interferon-alpha (IFN-alpha) administration in Wistar Han rats, and used the Wistar Kyoto (WKY) strain as an innate model of SSRI-resistant depression. Behavioural assessments included the forced swim test (FST; 15 min pre-test and 5 min test after 24h) and elevated plus maze (EPM), followed by molecular analyses of longitudinal plasma samples from tail vein blood, terminal cerebrospinal fluid (CSF) and medial prefrontal cortex (mPFC). Neuronal plasticity changes were assessed by measuring microtubule  $\alpha$ -tubulin post-translational modifications (PTMs), as marker of microtubule dynamics, and expression of key synaptic proteins including SV2A, synaptophysin, PSD-95 and spinophilin. IFN- $\alpha$  treatment increased immobility in the FST and reduced the time in open arm index, alongside reductions in pre- and post-synaptic proteins and microtubule dynamics. Compared to Wistar Han rats, vehicle-treated WKY rats show increased immobility in the FST. In both models, neither acute nor short-term fluoxetine (10 mg/kg, SC), the gold-standard SSRI, altered behavioural or molecular endpoints, in line with its chronic clinical efficacy. In contrast, a single dose of the NMDA receptor antagonist ketamine (5 mg/kg, SC) or the 5-HT<sub>2A</sub> agonist psilocybin (1 mg/kg, SC) reversed depressive-like behaviours and restored synaptic and structural plasticity markers. Both compounds shifted  $\alpha$ -tubulin PTMs towards a more dynamic microtubule state and selectively upregulated synaptic protein expression. We conclude that acute administration of ketamine and psilocybin produces rapid antidepressant-like effects in the IFN-alpha and WKY rats models of depression, highlighting their potential as fast-acting treatments targeting neuroplasticity and inflammatory pathways.

**Disclosures:** **E. Paschen:** A. Employment/Salary (full or part-time): Ulysses Neuroscience Ltd. **C. Maltby:** A. Employment/Salary (full or part-time): Ulysses Neuroscience Ltd. **J. Pinto:** A. Employment/Salary (full or part-time): Ulysses Neuroscience Ltd. **M. Bianchi:** A. Employment/Salary (full or part-time): Ulysses Neuroscience Ltd..

**Poster**

**PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.22/E29

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

**Support:** NRF-2022K1A3A1A20015190  
RS-2023-00302751  
RS-2024-00468036  
22RB1130

**Title:** Molecular mechanism of Trimethyltin induced cognitive deficits and neuroinflammation

**Authors:** \*S. SUN<sup>1,2,3</sup>, Y. JI<sup>1,2,3</sup>, E. SEO<sup>1,2,3</sup>, S. YU<sup>1,2,3</sup>, S. AHN<sup>1,2,3</sup>, H. SHIN<sup>4,5</sup>, S. PARK<sup>4,5</sup>, H. SEO<sup>1,2,3</sup>;

<sup>2</sup>Sch. of Bio-Pharmaceutical Convergence, College of Advanced Technol. and Convergence, <sup>3</sup>Ctr. for Bionano Intelligence Educ. and Research, Inst. for Precision Therapeut., <sup>1</sup>Hanyang Univ., Ansan, Korea, Republic of; <sup>4</sup>ETRI, Daejeon, Korea, Republic of; <sup>5</sup>Digital Bio Med. Res. Div., Electronics and Telecommunications Res. Inst., Daejeon, Korea, Republic of

**Abstract:** Trimethyltin (TMT), an organotin compound with a neurotoxicant, mainly damages the nervous system and is especially marked in the hippocampus region. TMT-induced neurodegenerative events like cognitive impairment and behavioral alterations are similar to Alzheimer's disease (AD) pathology. To understand the molecular mechanisms of TMT-induced neurotoxicity, C57BL/6 mice were administered with TMT (2.6 mg/kg/day, i.p. 2 weeks). After behavioral test to check cognitive function, transcriptomic analysis was performed next generation sequencing (NGS) with bulk RNA sequencing method using hippocampal tissues of experimental groups of mice. TMT mice showed significant deficits of learning and memory in the Morris water maze test similar to AD symptoms. Differentially expressed genes (DEGs) in TMT mice compared to control group mice include 167 genes (90 upregulated, 77 downregulated:  $\geq 2$ -fold,  $p < 0.05$ ). DEG data and behavior data analysis showed several candidate genes, including neuroinflammation/ neurodegeneration-related genes like Ccl5 and Mpeg1. Candidate genes were functionally validated using siRNA and agonists in hippocampal neurons supports these targets' roles in AD pathology. For example, after Mpeg1 siRNA transfection, the expression of mitochondrial dynamic related genes (Mfn1, Mfn2) was down-regulated in mouse hippocampal HT22 cells and microglial BV2 cells, suggesting that Mpeg1 gene may play a critical role in mitochondrial dynamics maintaining energy homeostasis during TMT-induced neuroinflammatory responses. In addition, TMT treatment increased the expression of inflammatory cytokines like IL-1 $\beta$  and TNF $\alpha$ , and also decreased cell viability in BV2 cells. This study suggests TMT-treated mice as a robust model of neurodegeneration with features similar to AD, especially for studying hippocampus-associated inflammation, memory impairment, and mitochondrial dysfunction.

**Disclosures:** S. Sun: None. Y. Ji: None. E. Seo: None. S. Yu: None. S. Ahn: None. H. Shin: None. S. Park: None. H. Seo: None.

**Poster**



## **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.23/E30

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Neuroinflammatory effects of S1, a subunit of the spike protein of SARS-CoV-2, in humanized mice

**Authors:** \*L. R. KESSLER<sup>1</sup>, M. G. FRANK<sup>2</sup>, C. A. LOWRY<sup>2</sup>;

<sup>1</sup>Intergrative Physiol., <sup>2</sup>Integrative Physiol., Univ. of Colorado Boulder, Boulder, CO

**Abstract:** The coronavirus disease of 2019 (COVID-19) caused a worldwide pandemic which still affects us today. The responsible virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel RNA virus that produces characteristic spike proteins that coat its outer membrane. In some cases, infection with SARS-CoV-2 can lead to Long COVID, where persisting and new symptoms last for weeks, months, or even years after the initial infection. While much research has been completed to understand how this virus affects us, there is still much to learn about why some cases of COVID-19 and Long COVID can result in neuroinflammation. Previous research has shown the spike protein of SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE-2) receptor on host cells, which not only facilitates viral entry, but could be linked to inflammation as well. In particular, the S1 subunit of the spike protein: 1) circulates in the bloodstream during infection; 2) can bind to ACE-2 independently; and 3) can even cross the blood-brain barrier (BBB). Here we examined neuroinflammatory effects of S1 application in humanized male mice expressing human ACE-2, K18-hACE-2 mice. Mice were given 10 µg of S1 via bilateral intranasal administration; 24 hours later mice were euthanized, and the prefrontal cortices and hippocampi were collected and flash-frozen in liquid nitrogen. RNA was isolated from tissue and relative gene expression was determined using real-time RT-PCR (reverse transcription polymerase chain reaction). We found that proinflammatory markers, *Nlrp3* and *Tlr4*, were significantly upregulated in the hippocampus and *Ifng*, which encodes the virus-associated cytokine IFN-γ, was significantly upregulated in the prefrontal cortex. The increase of *Nlrp3* and *Tlr4* supports previous research that shows S1 acts as an inflammatory PAMP (pathogen-associated molecular pattern), while the increase in *Ifng* shows it may be recognized as a viral PAMP. Future work will examine these effects at multiple acute time points and a week-long time point to get improved temporal resolution on cytokine release and long-term effects of S1-induced inflammation.

**Disclosures:** L.R. Kessler: None. M.G. Frank: None. C.A. Lowry: None.

### **Poster**

## **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.24/E31

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH/NICHD R01HD108015 (Manuzak)  
NIH/OD R21OD031435 (Manuzak)  
NIH/OD K01OD024876 (Manuzak)  
P51 OD011104 (TNPRC)

**Title:** Assessment of the effects of *Plasmodium fragile* malaria in pregnancy on neuroinflammation, blood-brain barrier integrity, and microglia morphology in the hippocampus of rhesus macaques.

**Authors:** \*J. PRUSAK, Jr<sup>1</sup>, S. FELL<sup>1</sup>, H. GREEN<sup>1</sup>, S. M. NEMPHOS<sup>1</sup>, L. DOYLE-MEYERS<sup>2</sup>, K. VAIL<sup>3</sup>, A. SAIED<sup>3</sup>, A. MACLEAN<sup>3</sup>, B. LONDONO<sup>4</sup>, J. MANUZAK<sup>1</sup>;  
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**Abstract:** Introduction: Pregnancy results in neuro-immune system alterations in neurogenic regions in the maternal brain, particularly the hippocampus, which may leave these sites vulnerable to damage during pathogen exposure. Here, we used a rhesus macaque (RM) model of malaria in pregnancy (MIP) to test the hypothesis that MIP will drive increased neuroinflammation, blood brain barrier (BBB) permeability, and microglia activation as compared to uninfected pregnant controls.

Methods: Pregnant RMs were inoculated with  $20 \times 10^6$  *P. fragile*-infected erythrocytes (n=5) or saline (n=6) during early- (gestational day [G]28), mid- (G65), and late-pregnancy (G100) followed by necropsy ~4 weeks post-inoculation (PI). Parasitemia was monitored by Giemsa-staining of thin blood smears. Anti-malarial drugs were administered when parasitemia exceeded 0.5%. Cytokine levels in cerebrospinal fluid (CSF) and hippocampal protein homogenates were assayed via a multiplex bead assay. BBB integrity, defined by zonulin and glut-1 co-expression, and microglia morphology, identified by Iba1 expression, were assayed on fixed-frozen hippocampus using immunofluorescent staining and digital quantification (HALO V3.6).

Results: Peak percent parasitemia (median=16%; range=13.01-57.50%) occurred by day 12 PI. Detectable levels of IP-10, IL-8, IL-6, and MCP-1 were observed in CSF and hippocampal protein homogenate. We observed a significant increase ( $p=0.0333$ ) in the levels of hippocampal IP-10 between RMs exposed to *P. fragile* MIP and uninfected controls at necropsy. No significant differences in CSF cytokine levels, BBB integrity, or microglia morphology were observed between *P. fragile* MIP RMs and control RMs at necropsy.

Conclusions: We observed elevated levels of IP-10 in the hippocampus of RMs exposed to *P. fragile* MIP compared to uninfected pregnant controls. However, alterations in CSF cytokines, BBB integrity, and microglia morphology in RMs with *P. fragile* MIP as compared to controls. These data suggest that MIP may induce neuroinflammation in the hippocampus but may not impact the neuro-vasculature or microglial morphology. These studies are ongoing, and additional animals are being assessed to allow for the interrogation of gestational date differences.

**Disclosures:** J. Prusak: None. S. Fell: None. H. Green: None. S.M. Nemphos: None. L. Doyle-Meyers: None. K. Vail: None. A. Saied: None. A. MacLean: None. B. Londono: None. J. Manuzak: None.

**Poster**

**PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.25/E32

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

**Support:** NINDS Grant RO1 NS110749

**Title:** Effects of High Fat Diet on Cognitive Function and Neuroinflammation Vary By Age of Menopause Onset

**Authors:** \*E. GROOM<sup>1</sup>, A. SALINERO<sup>2</sup>, C. ABI-GHANEM<sup>2</sup>, K. ZULOAGA<sup>2</sup>;  
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**Abstract:** Menopause is a major shift in endocrine function that occurs during mid-life in women. During menopause, ovarian follicular activity is decreased resulting in the loss of ovarian estrogens. This transition leaves women vulnerable to metabolic disease-associated cognitive decline. These metabolic alterations result in an increase in inflammation both peripherally and centrally which accelerates cognitive decline. However, how chronological aging influences cognitive and inflammatory outcomes during the menopause transition is poorly understood. We hypothesized that early-onset of menopause would exacerbate cognitive and inflammatory effects of a high fat diet. We used young-adult (2.5m old) and middle-aged (8m old) C57BL/6J female mice and modeled diet-induced obesity via chronic administration of high fat (HF) diet. We modeled menopause via injections of 4-vinylcyclohexene diepoxide, which causes accelerated ovarian failure. Behavioral testing was performed 7.5 months after diet onset, once mice had become acyclic (menopausal). We found that middle-aged onset of menopause greatly impaired spatial recognition memory when compared to young-adult onset. HF diet significantly impairing spatial recognition memory in both groups. Neuroinflammation was assessed via immunohistochemistry and hippocampal gene expression of pro-inflammatory receptors. The results showed an increase in neuroinflammatory markers in middle-aged mice compared to young-adult mice. These results suggest that middle-aged onset of menopause, especially when combined with a high-fat diet, leads to greater of cognitive impairment and neuroinflammation compared to young-adult onset. These findings highlight the need to consider age and metabolic status as key biological variables in menopause research, especially with regards to identifying critical windows to initiate interventions to prevent cognitive decline through the menopausal transition.

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**Poster**

## **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.26/E33

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Ideas Grant

**Title:** Epigenetic remodeling of sperm small RNAs by paternal chronic bacterial-like infection is associated with offspring anxiety and cognitive outcomes across generations

**Authors:** \*D. LU<sup>1,2</sup>, H. LIAO<sup>1,2</sup>, S. TSANG<sup>1,2</sup>, J. LAU<sup>2</sup>, S. N. REISINGER<sup>1,2</sup>, N. VAN DE GARDE<sup>1,2</sup>, A. J. HANNAN<sup>1,2,3</sup>;

<sup>1</sup>Univ. of Melbourne, Parkville, Australia; <sup>2</sup>Florey Inst. of Neurosci. and Mental Hlth., Parkville, Australia; <sup>3</sup>Univ. of Melbourne, Dept. of Anat. and Physiol., Parkville, Australia

**Abstract:** Emerging evidence suggests that paternal immune activation influences offspring brain development and behavior via epigenetic inheritance. This has been primarily studied in acute infection models. However, whether chronic paternal inflammation induces multigenerational phenotypic alterations and the mechanisms underlying these potential effects remain largely unexplored. Here, we established a chronic bacterial-like infection model by treating 8-week-old male C57BL/6J mice with weekly escalating lipopolysaccharide (LPS) injections over six weeks. Chronic immune activation was verified by significant weight loss, decreased food and water intake, and elevated clinical severity scores 24 hours post-injection. Four weeks after the final injection, allowing sufficient time for inflammation-induced epigenetic alterations to be integrated into the germline, treated F0 males were mated with naïve females. Sperm samples were then collected for comprehensive small-RNA profiling. Our results showed that offspring (F1) from LPS-treated sires exhibited reduced anxiety compared to controls, evidenced by increased exploration in the center zone of the open-field test, the open-arm of the elevated-plus maze, and the illuminated areas in the light-dark box. Female offspring also demonstrated improved object-recognition memory in the novel-object recognition test. This anxiolytic phenotype persisted in the subsequent generation (F2), indicated by male grand-offspring's decreased latency to feed in the novelty-suppressed feeding test. Small-RNA sequencing analysis of paternal sperm identified one significantly upregulated microRNA (miRNA), seven upregulated ribosomal-RNA-derived small RNAs (rsRNAs), two upregulated and one downregulated transfer RNA-derived small RNAs (tsRNAs). Functional gene ontology analysis revealed that the predicted target genes of these differentially expressed small RNAs are enriched for pathways involved in neural remodeling and synaptic transmission, potentially underlying the observed behavioral alterations. These findings provide novel mechanistic insights into how paternal chronic bacterial-like infection reshapes sperm small-RNA populations, specifically miRNAs, rsRNAs, and tsRNAs, to mediate multigenerational transmission of anxiety and cognitive phenotypes. Our data thus identify sperm-derived small RNAs as possible critical molecular mediators and promising therapeutic targets for preventing heritable 'epigenopathy'.

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**Poster**

**PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.27/E34

**Topic:** D.01. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant R01 NS-128086  
Lone Star Paralysis Foundation

**Title:** Extended graft storage time and surgical repair window for successful polyethylene glycol fusion repair of segmental-loss peripheral nerve injuries

**Authors:** \*L. ZHOU<sup>1</sup>, A. OLIVAREZ<sup>1</sup>, C. YANG<sup>1</sup>, A. SCHAFER<sup>1</sup>, G. PERIYASAMY<sup>1</sup>, V. GOKHALE<sup>1</sup>, A. AGARWAL<sup>1</sup>, R. SOOD<sup>1</sup>, H. GARCIA<sup>1</sup>, P. NGUYEN<sup>1</sup>, N. NAGARAJAN<sup>1</sup>, S. SANKLIPUR<sup>1</sup>, Y. HAO<sup>1</sup>, A. BHAT<sup>1</sup>, J. S. BUSHMAN<sup>2</sup>, G. D. BITTNER<sup>1</sup>;

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**Abstract:** Polyethylene glycol (PEG) fusion has consistently demonstrated success in repairing segmental-loss peripheral nerve injuries (SL-PNIs) in both small (rat) and large (pig) animal models. This technology immediately restores morphological and electrophysiological continuity across the lesion, prevents Wallerian degeneration (WD) of successfully fused axons, reinnervates many distal targets, and produces faster and better sensorimotor recovery compared to the clinical standard of neuroorrhaphy alone. Importantly, PEG-fused allografts produce behavior recovery comparable to PEG-fused autografts and are not immunologically rejected, making them a promising alternative to autografts. However, two challenges to clinical translation remain: the limited availability of freshly harvested donor nerves and a limited surgical repair window due to WD. Our prior work addressed many of these challenges by demonstrating successful PEG-fusion using viable peripheral nerve allografts (VPNAs) stored for up to 5 days and repairing at 1 day post operation (dpi). In the current study, we extend these findings by demonstrating successful PEG-fusion under more clinically relevant conditions, including longer *ex vivo* VPNA storage time of at least 3 weeks and/or delayed repairs up to 3 dpi. In all cases, Lewis rats exhibited significantly improved motor function by 8 weeks postoperatively, as assessed by the Sciatic Functional Index, whereas Negative Controls (neuroorrhaphy without PEG application) showed no recovery. We demonstrate our refined protocols for allograft storage and surgical procedures that minimize intraoperative bleeding associated with poorer outcomes. Our data support the development of donor VPNA tissue banks and the clinical practicality of PEG-fusion to repair SL-PNIs within an acceptable surgical window.

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**Poster**

**PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.28/E35

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

**Support:** NIH P20GM148302  
NIH RF1 NS083559  
RF1 NS10457

**Title:** Discovery of a Ventral Meningeal Lymphatic Outflow Hub Surrounding the Human Middle Meningeal Artery

**Authors:** \*O. ALBAYRAM;

Dept. of Pathology and Dept. of Neurosci., Med. Univ. of South Carolina, Charleston, SC

**Abstract:** The anatomical and functional routes of cerebrospinal and interstitial fluid (CSF-ISF) clearance in the human brain remain incompletely mapped—especially along ventral dural surfaces, where meningeal lymphatic contributions are poorly understood. In this study, we provide the first in vivo and ex vivo evidence of a structurally distinct lymphatic drainage system surrounding the human middle meningeal artery (MMA), establishing the ventral skull base as a critical CSF-ISF outflow zone. Using dynamic contrast-enhanced MRI in five healthy adults, we uncovered a delayed, region-specific signal enhancement in the periphery of the MMA that peaked at 90 minutes post-injection—substantially later than classical vascular or lymph node responses. This distinct kinetic signature suggested slower, lymphatic-like fluid dynamics. To anatomically validate this finding, we conducted high-resolution histological profiling of dorsal and ventral MMA-adjacent dura using two orthogonal platforms: confocal immunofluorescence and Hyperion™ Imaging Mass Cytometry (IMC). Together, these modalities revealed a robust lymphatic network in the ventral dura enriched with PROX1+, PDPN+, and LYVE1+ vessels, with spatially stratified orientations across dural layers. We further identified lymphatic elements embedded within the tunica media of the MMA arterial wall, and mesenchymal-like PROX1+/PDPN+ structures at the periosteal-bone interface—features suggestive of novel perivascular or skull-interfacing lymphatic roles. Notably, LYVE1 expression was sparse and discontinuous compared to PROX1 and PDPN, pointing to phenotypic heterogeneity among meningeal lymphatic endothelial cells. This study introduces the first spatial proteomic mapping of human meningeal lymphatics using IMC and defines a previously unrecognized ventral clearance pathway adjacent to the MMA. Our findings revise the anatomical atlas of CSF-ISF

drainage in the human brain and open new directions for investigating how meningeal lymphatic architecture contributes to neuroimmune homeostasis and disease vulnerability.

**Disclosures:** O. Albayram: None.

## **Poster**

### **PSTR213: Neuroinflammation in Animal Models**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR213.29/E36

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

**Title:** Toward a 2-Hit Model of Delirium: Behavioral and Electrophysiological Signatures of Systemic Inflammation Across Diverse Vulnerability States in Mice

**Authors:** \*T. MEHTA<sup>1</sup>, E. Y. KIMCHI<sup>2</sup>, T. KIM<sup>4</sup>, S. STATEN-LUSTY<sup>2</sup>, R. PALKAR<sup>3</sup>, V. IM<sup>3</sup>, J. AMETOVSKI<sup>3</sup>, M. MARROQUIN<sup>3</sup>;

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**Abstract:** Delirium is an acute neuropsychiatric disorder often triggered by acute insults in patients with underlying brain vulnerability. Yet, robust translational models for this “2-hit” framework remain limited. Here, we evaluated systemic inflammation as a precipitant across multiple predisposing phenotypes including amyloidosis, tauopathy, and aging using behavior and in-vivo electrophysiology. We studied three experimental groups: aged WT (15-22 months) mice vs. young WT (4-6 months), 5xFAD (amyloidosis model) vs. age-matched WT controls, and Tau PS19 (tauopathy model) vs. age-matched WT controls. Systemic inflammation was induced via 0.5 mg/kg intraperitoneal lipopolysaccharide (LPS); saline served as control. Mice were monitored continuously using home cage video for 72 hours post-injection. Behavioral endpoints included locomotion and nesting, analyzed using Camus, our custom video analysis pipeline. EEG/EMG was recorded to assess arousal patterns and slow-wave activity changes. LPS-induced hypoactivity and nesting disruption across all groups but was most severe and prolonged in Tau PS19 mice. EEG following LPS administration revealed disrupted circadian rhythmicity and a shift in spectral power toward lower frequencies and was more evident during the dark phase. These findings support the utility of Tau PS19 mice as high-sensitivity models for studying delirium as a 2-hit phenomenon. Comparative analysis across vulnerabilities reveals both shared and divergent behavioral and neural responses to systemic inflammation. These models offer a promising platform for elucidating delirium pathophysiology and testing targeted interventions. Ongoing studies will further explore model reliability, mechanistic pathways, and recovery dynamics.

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E.Y. Kimchi: A. Employment/Salary (full or part-time): Northwestern University. T. Kim:

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## Poster

### PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.01/

**Topic:** D.03. Stroke

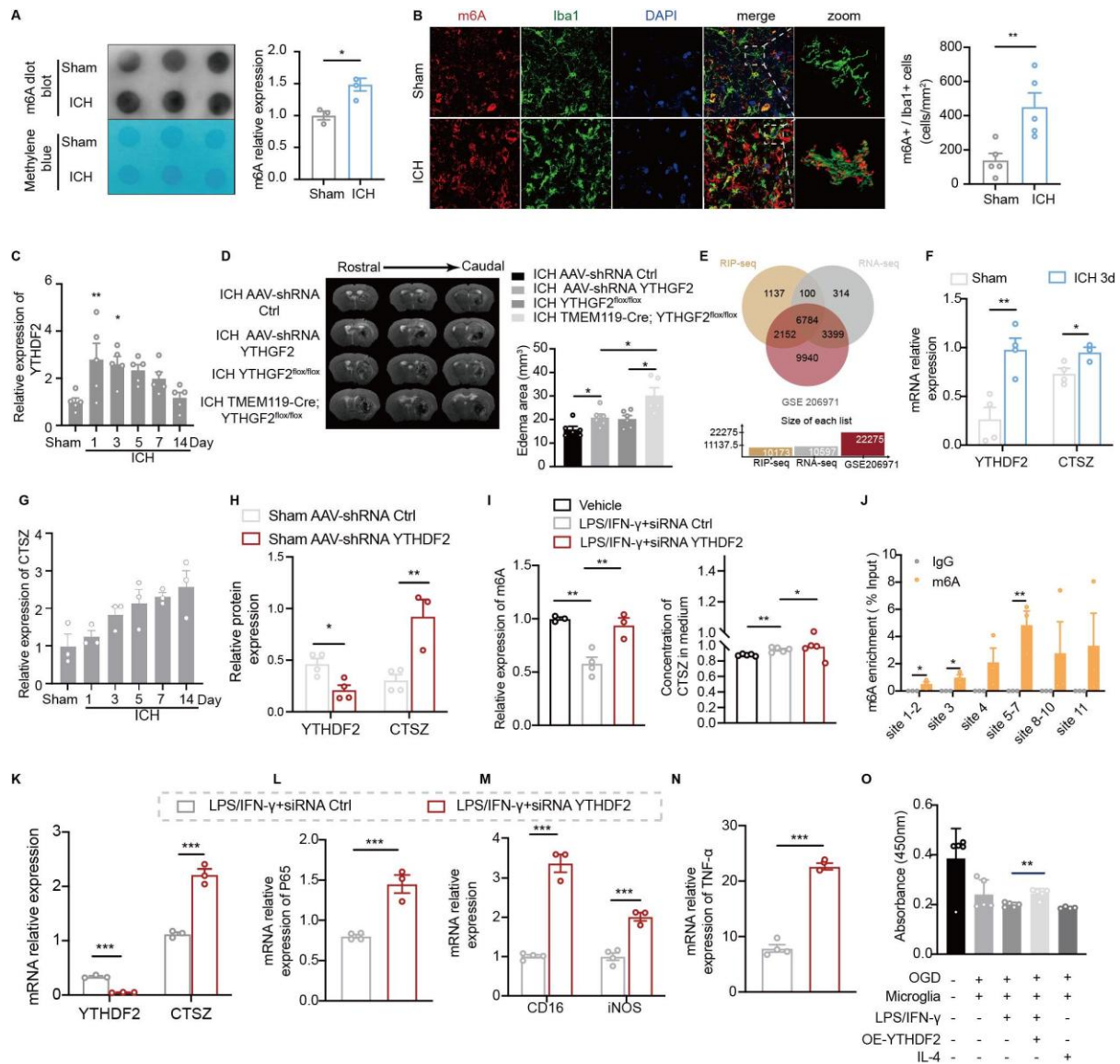
**Support:** National Natural Science Foundation of China (Grant No. 82171268)  
National Natural Science Foundation of China (Grant No. 81871021)

**Title:** The m6A reader YTHDF2 deficiency exacerbates neuroinflammation and cognitive deficits after intracerebral hemorrhage via cathepsin Z activation

**Authors:** \*Y. ZHENG, W. YE, S. ZHAO, S. WEN, W. DONG, Q. CHEN, X. LIU;  
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**Abstract:** **Aim** N6-methyladenosine (m6A) is the most prevalent mRNA modification and plays a critical role in regulating immune responses. However, the function of the m6A reader YTHDF2 in intracerebral hemorrhage (ICH) remains unclear. This study aimed to explore the role of YTHDF2 function in ICH and its underlying mechanisms. **Methods** Microglia were isolated from ICH mice, and the levels of m6A and YTHDF2 were evaluated using qRT-PCR, Western blot, and immunofluorescence. Ythdf2 loss-of-function models were established via Tmem119-Cre mice and AAV-mediated knockdown. Brain edema and neurological deficits were assessed by MRI and behavioral tests. RNA-seq and RNA immunoprecipitation sequencing were performed to identify YTHDF2-regulated targets, which were further validated through molecular assays and microglia-neuron co-culture experiments. **Results** m6A levels increased in microglia after ICH, accompanied by elevated YTHDF2 expression. Immunofluorescence confirmed enhanced co-localization of YTHDF2 with microglia. YTHDF2 deficiency exacerbated brain edema, particularly in the Tmem119-Cre model. During the subacute phase, YTHDF2-deficient mice exhibited cognitive impairments in novel object/location recognition and spatial memory. Cathepsin Z (CTSZ) was identified as a critical YTHDF2-bound target. YTHDF2 knockdown led to CTSZ accumulation, activation of NF- $\kappa$ B signaling, and increased expression of proinflammatory markers such as TNF- $\alpha$  and CD16. Furthermore, YTHDF2 overexpression protected neurons from injury in an oxygen-glucose deprivation (OGD) model. **Discussion** In summary, YTHDF2 protects against neuroinflammation and cognitive deficits after ICH by destabilizing CTSZ mRNA, subsequently inhibiting NF- $\kappa$ B pathway activation and suppressing microglial overactivation. These findings suggest that targeting the m6A-YTHDF2-CTSZ axis may represent a promising therapeutic strategy for ICH.





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**Poster**

**PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.02/E37

**Topic:** D.03. Stroke

**Support:** NIH/NINDS R01-NS101013  
NIH T32-GR0019882  
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NIH/NINDS T32-NS126157  
NIH/NIBIB P41-EB018783  
NIH/NIBIB R01-EB026439  
NIH/NINDS U24-NS109103

**Title:** Motor impairment and adaptation in a novel non-human primate model of internal capsule infarct

**Authors:** \*S. S. SIVAKUMAR<sup>1,2</sup>, S. A. ANAND<sup>1,2</sup>, L. BRAWER<sup>2</sup>, R. L. MELLOR<sup>3</sup>, A. BURKHALTER<sup>3</sup>, H. BURTON<sup>3</sup>, P. BRUNNER<sup>1,4,5</sup>, D. T. BUNDY<sup>1,4,5</sup>, E. C. LEUTHARDT<sup>1,4,5</sup>, D. W. MORAN<sup>1,3,5</sup>;

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**Abstract:** Loss of distal hand and finger control is among the most disabling consequences of stroke. Functional outcomes are typically worse when infarcts involve subcortical white matter tracts, particularly the internal capsule, yet most preclinical stroke models target cortical regions. To address this gap, we developed a non-human primate model of internal capsule infarct using stereotactically guided endothelin-1 injections to disrupt descending fibers from the primary motor cortex hand area. Serial structural and diffusion MRI, along with histology, confirmed subcortical infarcts centered on the targeted white matter region with no apparent cortical involvement. Motor function was assessed pre- and post-infarct using a joystick-based center-out task (proximal forelimb control) and a Klüver board task (distal forelimb control). Animals exhibited variable impairments in proximal function and consistent post-infarct deficits in distal function, including reduced contralesional hand use, longer retrieval time, and increased in-well digit flexions. One animal showed mild post-infarct impairment and the smallest lesion, highlighting that this model reflects inter-individual differences in infarct size and functional outcome as seen in human subcortical stroke. In contrast, the other two animals developed a compensatory wrist-extended posture on the Klüver board task by 4 weeks post-infarct, which stabilized the hand and enabled improved digit flexion. Incorporating this behavioral adaptation into statistical models improved prediction of motor performance. The observed adaptation may have drawn on spared corticospinal output pathways, allowing animals to re-engage pre-existing motor routines to perform the retrieval. While future studies may benefit from ethologically relevant tasks to further elucidate such adaptations, findings from this study recapitulate key features of human subcortical stroke, including persistent distal motor deficits and emergence of adaptive motor strategies. By combining precise lesioning, longitudinal imaging, and detailed behavioral analysis, this model provides a translationally oriented platform for studying white matter stroke mechanisms and evaluating interventions that promote functional recovery.

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Neuroscience, Inner Cosmos, Aurenar, Petal Surgical, Inflexion Vascular, Cordance Medical, Silent Surgical, Intellectual Ventures. F. Consulting Fees (e.g., advisory boards); Monteris Medical, E15, Neuroolutions. **D.W. Moran:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuroolutions, Inner Cosmos.

## **Poster**

### **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.03/E38

**Topic:** D.03. Stroke

**Support:** NIH Grant R01NS030853  
NIH Grant F32NS100339  
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the Landon Center on Learning

**Title:** Distinct alterations in neural activity associated with motor recovery following cortical (M1) and subcortical (internal capsule) lesions in rodents

**Authors:** \***P. E. CETTINA**<sup>1,2</sup>, D. J. GUGGENMOS<sup>4</sup>, S. S. SIVAKUMAR<sup>2</sup>, P. DEMAREST<sup>2</sup>, M. D. MURPHY<sup>6</sup>, S. BARBAY<sup>4</sup>, R. J. NUDO<sup>4,5</sup>, D. T. BUNDY<sup>3,2</sup>;  
<sup>2</sup>Biomed. Engin., <sup>3</sup>Neurolog. Surgery, <sup>1</sup>Washington Univ. in St. Louis, St. Louis, MO; <sup>4</sup>Rehabil. Med., <sup>5</sup>Landon Ctr. on Aging, Univ. of Kansas Med. Ctr., Kansas City, KS; <sup>6</sup>Bioengineering, Univ. of Kansas, Lawrence, KS

**Abstract:** Each year, over three-quarters of a million Americans suffer from stroke, often leading to persistent motor impairments. Although the locations and extent of infarcts are heterogeneous, motor deficits are most associated with damage to subcortical white matter structures. Unfortunately, these subcortical regions are largely underrepresented in preclinical models of stroke. Furthermore, the direct link between motor recovery and its associated neural activity is uncertain. To investigate the neurophysiological response to strokes in distinct locations, a photothrombotic stroke model was employed to target either cortical (M1) or subcortical (internal capsule or IC) regions. Long-Evans rats (n=14) were trained on a complex reaching task combining ‘gross’ (button press) and ‘fine’ (pellet retrieval) reaching tasks. Following training rodents were randomized into one of three groups: control (n=3), cortical infarct (n=5), or capsular infarct (n=5). Rodents underwent surgery to induce lesions and implant 3 chronic, 16-channel microelectrode arrays in the ipsilesional hemisphere targeting the rostral forelimb area (RFA or rodent pre-motor), CFA (M1), and primary somatosensory areas (S1). Following surgery, rodents participated in biweekly sessions (over 8 weeks) performing the complex task while neural data were simultaneously recorded. Compared to control animals, both lesion groups showed a decline in success rate relative to their pre-infarct baseline, though the time course of recovery differed significantly between the groups ( $p < 0.001$ ). Interestingly,

analysis of the reach-to-grasp interval (the time between initiation of reach and grasp) revealed that, following recovery, the cortical group took significantly longer to execute individual reaches ( $p < 0.001$ ) while the capsular group were not significantly different from control animals. Control animals maintained stable neural firing activity across sessions, while both stroke groups exhibited attenuated neural activity during task epochs. After recovery plateaued, the cortical group showed more pronounced alterations in neural firing across sensorimotor regions ( $p < 0.01$ ), particular during task periods immediately surrounding the onset of reach and grasp ( $p < 0.001$ ,  $p < 0.01$ ). In contrast, rodents with an internal capsule infarct did not show a significant reduction in cortical firing compared to controls ( $p = 0.0702$ ). These results suggest distinct mechanisms of post-stroke neural reorganization that depend on lesion location. This highlights the potential need for patient-specific rehabilitation strategies after stroke.

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## **Poster**

### **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.04/E39

**Topic:** D.03. Stroke

**Support:** Nix Family Foundation Scholarship  
Presidential Graduate Research Fellowship

**Title:** Sensory challenge increases postural sway in acute stroke survivors without altering frequency signatures

**Authors:** \*M. MEYER VEGA<sup>1</sup>, N. ALSALMIE<sup>1</sup>, V. ROBLES-CERDAS<sup>1</sup>, N. SHAH<sup>1</sup>, N. VALADI<sup>3</sup>, H. S. BAWEJA<sup>2</sup>;

<sup>2</sup>Doctor of Physical Therapy Program, <sup>1</sup>Auburn Univ., Auburn, AL; <sup>3</sup>Neurol. Ctr. of East Alabama, Opelika, AL

**Abstract:** Stroke survivors face an elevated fall risk, with 7% falling within the first week and up to 73% within the first-year post-stroke. Effective postural control requires integration of visual, proprioceptive, and vestibular inputs; yet the extent to which sensory interaction is disrupted following stroke remains poorly understood, particularly in the acute phase of recovery. Understanding how stroke alters sensory integration is critical for developing targeted interventions to reduce fall risk and support functional independence. We investigated how individuals with acute stroke process and integrate sensory information for postural control compared to age-matched healthy controls. Twenty-seven participants (15 acute stroke and 12 age-matched healthy controls (HC)) volunteered to participate in the study. Each participant

completed four postural tasks on a force plate: quiet standing with eyes open (baseline), eyes closed to isolate visual input, eyes open on foam to challenge proprioception, and eyes closed on foam to assess vestibular reliance. Postural sway was measured linearly in the anterior-posterior (AP) and medial-lateral (ML) directions, as well as by total center of pressure (COP) displacement over 20 seconds. Continuous wavelet transform was used to analyze low-frequency oscillations in the postural sway signal from 0-4 Hz. We found that: 1) Acute stroke survivors demonstrated significantly greater AP ( $p = 0.023$ ) and total COP sway displacement ( $p = 0.011$ ) when compared with HC; 2) Postural sway displacement and low-frequency oscillations in AP, ML, and total COP increased progressively across task conditions from baseline < visual < proprioceptive < vestibular ( $p < 0.001$ ); 3) Over 80% of the spectral power concentrates within the 0-1 Hz frequency bin across the AP, ML, and total COP wavelet spectrums ( $p < 0.001$ ); 4) Similarly, spectral density was predominantly concentrated in 0-1 Hz bin for the visual, proprioceptive, and vestibular conditions ( $p < 0.001$ ), and this difference was more pronounced with increasing task difficulty. Despite task-related changes, no significant group differences were observed in low frequency oscillations. While stroke survivors exhibit increased postural sway, preserved frequency patterns suggest that sensory interaction mechanisms remain intact in the acute stages of recovery. It has been suggested that specific frequency bins from 0-1 Hz correspond to different sensory inputs: visual (0-0.1 Hz), vestibular (0.1-0.5 Hz), and proprioceptive (0.5-1 Hz). Future studies should investigate these low-frequency oscillations to understand sensory interaction during recovery in acute stroke survivors.

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## **Poster**

### **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.05/E40

**Topic:** D.03. Stroke

**Support:** NIH R01NS064136C (GKS)  
R01NS093057 (GKS)  
R01NS058784 (GKS)  
AHA Postdoctoral Fellowship 916011 (HC)  
AHA Career Development Award 24CDA1266810 (HC)

**Title:** Rapid Endothelial Glycocalyx Loss and Vascular Complement Activation in Hyperglycemic Stroke

**Authors:** \*H. CHEN<sup>1</sup>, J. FRANK<sup>5</sup>, C. TAN<sup>6</sup>, A. G. LEE<sup>7</sup>, R. KOPCHOCK, III<sup>2</sup>, T. C. CHIANG<sup>2</sup>, A. KIM<sup>2</sup>, M. GALVAN<sup>8</sup>, J. F. FRASER<sup>9</sup>, D. DORNBOS III<sup>10</sup>, H. ABOUL-NOUR<sup>5</sup>, S. TOMLINSON<sup>11</sup>, L. D. MCCULLOUGH<sup>12</sup>, K. R. PENNYPACKER<sup>13</sup>, M. Y. CHENG<sup>2</sup>, T. BLISS<sup>3</sup>, G. K. STEINBERG<sup>4</sup>;

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**Abstract: Background:** Acute hyperglycemia, affecting ~40% of stroke patients, worsens outcomes despite standard glucose control, yet no targeted therapy exists. We examined the role of the cerebral vascular lumen in hyperglycemia-exacerbated stroke injury in mice and humans, focusing on luminal glycocalyx and vascular complement activation. **Method:** Male C57BL/6 mice (10-11 weeks) underwent 30 min transient MCAO followed by reperfusion to mimic thrombectomy. Hyperglycemia was induced by glucose injection 10 min before occlusion, raising glucose ~2-fold, matching patients' fold change. Mice were assessed at multiple time points for BBB disruption (Evans blue, IgM/IgG staining), neurological deficits, motor function (open field), and mortality. Glycocalyx disruption was evaluated by electron microscopy and IB4 staining; complement activation was assessed by C3d staining. The role of complement C3 was assessed using C3 knockout mice and a site-targeted C3 inhibitor CR2-Crry. Outcomes were assessed by experimenters blinded to group. Human stroke and control post-mortem brain tissues (n=5/group; mean age: 68.6 vs. 69.2) were analyzed using UEA I lectin (glycocalyx) and C3d/IgG immunostaining. Additionally, patient pre-thrombectomy plasma samples (n=66) were analyzed via elastic net regression to assess if complement biomarkers predict outcomes. **Result:** Within 4.5 hours of stroke, hyperglycemia disrupted the endothelial glycocalyx, accompanied by luminal IgM/IgG deposition, vascular C3 activation, and BBB leakage (n=5, p<0.0001) - these changes were absent in normoglycemic stroke mice. Complement activation persisted after glucose normalization and was exacerbated by reperfusion, propagating complement activation into the brain. This early vascular damage increased mortality (100% vs. 25%, p=0.0008) and worsened neurological deficits (p<0.001). C3 knockout mice showed reduced BBB leakage (n=6, p<0.01) and less functional deficit (p<0.01), supporting a causal role for complement C3. Site-targeted complement inhibition with CR2-Crry at 30 min post-reperfusion preserves BBB integrity and reduces functional deficit (n=4, p<0.01), providing proof-of-concept for complement-targeted therapy. In human stroke brain tissue, C3 activation colocalized with luminal glycocalyx loss. Circulating complement activation markers (Ba, Bb, C4a, C3a) in pre-thrombectomy plasma independently predicted modified Rankin Scale (mRS) outcomes. **Conclusion:** We identify a rapid Metabolic-Complement-Vascular (MCV) axis that drives hyperglycemia-exacerbated stroke injury. These findings support C3 inhibition as an adjunct therapy to thrombectomy.

**Disclosures:** H. Chen: None. J. Frank: None. C. Tan: None. A.G. Lee: None. R. Kopchok: None. T.C. Chiang: None. A. Kim: None. M. Galvan: None. J.F. Fraser: None. D. Dornbos III: None. H. Aboul-Nour: None. S. Tomlinson: None. L.D. McCullough: None. K.R. Pennypacker: None. M.Y. Cheng: None. T. Bliss: None. G.K. Steinberg: None.

**Poster**

**PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.06/E41

**Topic:** D.03. Stroke

**Support:** VA I01BX006894 (DS & SYC)  
VA IK6BX005647 (DS)  
WoodNext Foundation (SYC)

**Title:** Ncoa7 deficiency exacerbates brain injury and increases post-stroke mortality in mice

**Authors:** \*K. KALIYAPPAN<sup>1,4</sup>, S. SONG<sup>2,4,5</sup>, Y. SHI<sup>3</sup>, Y. TANG<sup>3</sup>, S. ROSE<sup>6</sup>, V. FIESLER<sup>2</sup>, K. HE<sup>2</sup>, S. CHAN<sup>3</sup>, D. SUN<sup>2,4,5</sup>;

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**Abstract: Background:** Lysosomal acidification, driven by vacuolar H<sup>+</sup>-ATPase (V-ATPase), is essential for neuronal homeostasis. Nuclear receptor coactivator 7 (Ncoa7), a TLDc domain-containing protein, directly binds and modulates V-ATPase assembly. Recent findings show that NCOA7 deficiency disrupts lysosomal acidification and increases inflammatory stress in endothelial cells and neurons. This alters synaptic development and leads to behavioral abnormalities. In this study, we investigated whether Ncoa7 deficiency increases susceptibility to stroke-mediated brain injury. **Methods:** Wild-type (WT) and Ncoa7 knockout (Ncoa7-KO) mice (adult, male and female) were subjected to transient left middle cerebral artery occlusion (tMCAo) to induce ischemic stroke. Post-stroke neurological function deficit, cerebral blood flow (CBF), and pathological brain damage were assessed. **Results:** Wild-type (WT) stroke mice displayed 100% survival rate within 48 hours acute post-stroke period. In contrast, despite a transient CBF increase post-MCAo, Ncoa7-KO mice exhibited significantly higher mortality, worsened neurological deficit and larger infarct volumes. Histopathological analyses revealed substantial blood-brain barrier (BBB) leakage, increased astrogliosis, and heightened microglial activation in the Ncoa7-KO stroke brains. Compared to male Ncoa7-KO mice, female Ncoa7-KO stroke mice showed significantly greater body weight loss (p<0.05) and neurological deficits, accompanied by decreased levels of lysosomal marker LAMP1 and the neuronal microtubule-associated protein 2 (MAP2). But compared to the WT stroke mice, both male and female Ncoa7-KO stroke mice displayed significant increase in V-ATPase ATP6V1B2 subunit levels but lower LAMP1 expression. **Conclusion:** NCOA7 plays an essential role in preserving brain tolerance to ischemic stroke-mediated brain damage. Both male and female Ncoa7-KO mice exhibited increased mortality and infarct severity. In females, Ncoa7 deficiency leads to more pronounced neurological deficits, associated with reduced expression of key neuronal structural MAP2 protein and lysosomal LAMP1 expression. Additional studies are warranted to elucidate how NCOA7 deficiency interrupts lysosomal integrity without altering the V-ATPase subunit expression and different susceptibility displayed in male and female mice.

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**Poster**

**PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.07/E42

**Topic:** D.03. Stroke

**Title:** Interferon- $\gamma$  contributes to sexual dimorphism in regulatory T cell fragility after ischemic stroke

**Authors:** \*J. SHAN, F. XU, X. HU;  
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**Abstract:** Ischemic stroke is a leading cause of death and long-term disability. CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells (Tregs) are a specialized subpopulation of T cells that play essential roles in suppressing inflammatory responses and maintaining immune homeostasis following ischemic stroke. Adoptive transfer of allogeneic male Tregs can reduce brain infarct in young male recipient mice during the acute stages of stroke. However, the contribution of Tregs in female stroke mice are not characterized. The clinical application of Tregs as a cell therapy is restricted by their low abundance and instability in an inflammatory environment. In this study, we investigated a mechanism that impact Treg stability, which underlies the sexual dimorphisms in Tregs. Stroke was induced by 60 min tMCAO in male or female (10-week) wild type mice and DTR mice expressing the diphtheria toxin receptor under the control of Foxp3 promoter. MRI and immunostaining demonstrated that Tregs depletion resulted in enlarged brain infarct and deteriorated sensorimotor functions in young female mice, while showed no significant effect on young male mice, cancelling out sex differences in acute ischemic brain injury. A series of adoptive transfer experiments using the same low dose of Tregs showed that only Tregs prepared from young female mice, but not those from young male provided neuroprotection at a low dose to young male stroke mice. RNA-seq analysis of Tregs sorted from blood 5d after tMCAO surgery showed that interferon (IFN)  $\gamma$  signalling was downregulated in female Tregs compared to male Tregs, suggesting a sex difference in Treg-mediated immune response after stroke. We further confirmed that IFN $\gamma$  treatment led to Treg fragility, which was characterized by reduced expression of CD39, Helios and Nr1 through flow cytometry. Collectively, our studies suggest activation of IFN $\gamma$  signaling increases Treg fragility and impairs their immunosuppressive function, which contributes to the sexual dimorphism in stroke outcomes. IFN $\gamma$  neutralization may represent an adjuvant therapy to lower the dose of Treg and improve their therapeutic effects.

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**Poster**



## **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.08/E43

**Topic:** D.03. Stroke

**Title:** Characterizing Upper Extremity Coordination Post-Stroke in Real-World Conditions: A Polar Coordinate Approach with Wearable Accelerometers

**Authors:** \*Y. MINAMIKAWA<sup>1</sup>, Y. NISHI<sup>2,3</sup>, S. MORIOKA<sup>2</sup>;

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**Abstract:** Upper extremity (UE) impairment following stroke often results in asymmetric movement patterns in free-living conditions, with reduced use of the paretic limb linked to diminished quality of life. While wrist-worn accelerometers are commonly used to assess UE activity, they provide limited insight into coordination between the forearm and upper arm. This study aimed to characterize post-stroke upper limb coordination using wrist- and upper-arm-worn accelerometers under free-living conditions. Fifty-two subacute stroke survivors (mean age:  $71.7 \pm 11.7$ ) and 30 older adults without UE impairment (mean age:  $80.1 \pm 9.9$ ) wore inertial sensors (Axivity AX6) on the wrist and upper arm of both UEs for 24 hours. Vector magnitude (VM) was calculated for each segment, and the difference in VM ( $\Delta VM$ ), defined as paretic minus non-paretic VM, was computed for the forearm and upper arm. Polar coordinate transformation was applied to derive directional angles ( $\theta$ ) between segmental  $\Delta VM$ s, representing intersegmental coordination. These were converted to degrees (0-360°) and classified into four directional zones. Specifically, 0°-90° indicated co-activation of the paretic UE, and 180°-270° indicated co-activation of the non-paretic UE. The proportion of  $\theta$  values within each zone was calculated. Additionally, mean  $\theta$  (reflecting forearm-upper arm imbalance), a concentration parameter (indicating directional consistency), and Ashman's D (a measure of distribution modality;  $D \geq 2$  indicates bimodality) were analyzed. Group differences were assessed using Mann-Whitney U tests ( $\alpha = 0.05$ ). Stroke survivors showed a significantly higher proportion of activity in the 180°-270° zone ( $p < 0.01$ ), indicating greater reliance on the non-paretic UE. No differences were found in the other zones. Mean  $\theta$  was shifted in the stroke group, reflecting asymmetry in coordination. Ashman's D was significantly higher among stroke participants ( $p < 0.01$ ), indicating a mixed unimodal-bimodal distribution, while controls showed consistent bimodality. The concentration parameter was also higher in the stroke group ( $p < 0.01$ ), suggesting stereotyped patterns and reduced motor flexibility. These findings highlight impaired coordination and fixed compensatory strategies post-stroke. Preserved activity in the 0°-90° zone may reflect residual function. This polar coordinate method offers a novel approach to quantifying real-world UE coordination, providing objective metrics for monitoring recovery and personalizing rehabilitation strategies aimed at restoring balanced and flexible UE activity patterns.

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## Poster

### PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.09/E44

**Topic:** D.03. Stroke

**Support:** NIH Grant HD58301  
NIDILRR funded Rehabilitation Engineering Research Center grant  
90RE5021

**Title:** Hand dominance influences motor recovery trajectories following stroke: a kinematic study

**Authors:** \*J. GUTTERMAN<sup>1</sup>, G. FLUET<sup>1</sup>, Q. Z. QIU<sup>1</sup>, J. PATEL<sup>1</sup>, H. GORIN<sup>1</sup>, K. KARUNAKARAN<sup>3</sup>, K. J. NOLAN<sup>3</sup>, E. KAPLAN<sup>3</sup>, A. MONT<sup>2</sup>, A. MERIANS<sup>1</sup>, S. V. ADAMOVICH<sup>4</sup>;

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**Abstract:** Stroke often causes persistent upper extremity (UE) motor deficits, particularly in reaching and grasping, impacting daily activities. Recovery patterns may depend on whether the affected hand is the individual's dominant or non-dominant hand, a distinction that is understudied. While clinical assessments are commonly used, kinematic analysis, which quantifies movement characteristics, may provide a more sensitive approach to detect nuanced changes in motor control during the critical early recovery period. The objective of the study was to investigate how UE recovery differs depending on hand dominance of the affected hand post-stroke. 10 participants with stroke affecting their dominant hand (mean age = 54.4; males = 6) and 10 with their non-dominant hand affected (mean age = 63.7; males = 5) performed reach to grasp tasks with two small objects (1 inch cube, 2.5 inch circular object) and clinical assessments over six months. Clinical assessments included the Box and Block Test, Upper Extremity Fugl-Meyer Assessment, and Action Research Arm Test. Kinematic variables included proximal function (time to peak velocity, smoothness, trajectory ratio), distal function (grasp duration, time after peak velocity) and combined function (reach duration). Trajectories were modeled at days 15, 30, 45, 60, 120, and 180 post-stroke using cubic splines and piecewise linear mixed-effects models, with Holm-Bonferroni correction. While both groups showed significant improvements in clinical measures during the first 45 days post-stroke (all  $p < .05$ ), only the affected dominant hand group showed early improvements in kinematic measures. The affected dominant hand group had significant early improvements in all proximal measures, one distal measure (time after peak velocity) and combined function. The affected non-dominant hand group did not show significant improvement in any kinematic variable at any time point (all  $p > .05$ ). Grasp duration remained non-significant for both groups. The results demonstrated kinematics reveal neural recovery patterns that are concealed by clinical measures. Significant

kinematic improvements occurred only when the dominant hand was affected, likely reflecting reliance and motivation to use the dominant hand during daily activities. The affected non-dominant hand group did not show significant kinematic improvement, potentially due to continued use of the unaffected dominant hand and its typical stabilizing role. These findings highlight the need for rehabilitation strategies tailored to the functional role of the affected hand, such as incorporating bimanual or stabilization tasks when the non-dominant hand is impaired.

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## **Poster**

### **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.10/E45

**Topic:** D.03. Stroke

**Support:** NIH Grant R01 NS120226

**Title:** Lateralization of Pupil Diameter in Stroke at Rest and During Hand Opening Compared to Controls

**Authors:** \*M. SEREIKA<sup>1</sup>, A. CHANG<sup>2</sup>, J. Z. SHAO<sup>2</sup>, J. P. DEWALD<sup>2</sup>, J. YAO<sup>2</sup>;

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**Abstract:** Background: Following a stroke affecting upper limb function, descending cortical drive from the lesioned hemisphere is reduced. This may alter input to neuromodulatory centers such as the locus coeruleus (LC), which consists of bilateral nuclei in the brainstem that release norepinephrine (NE) throughout the nervous system. Prior research from our lab suggests that decreased cortical inhibition of the LC post-stroke may lead to increased and lateralized NE release. This may amplify contralesional, ipsilateral neural pathways to the paretic upper limb, contributing to flexion synergy and impaired motor control. Direct measurement of LC activity in humans is challenging, but pupil diameter (PD) offers a non-invasive proxy of LC-driven noradrenergic activity. Prior studies in rodents have shown that LC stimulation produces lateralized effects, with greater PD increases ipsilateral to the stimulated LC. We propose that PD is a promising tool to investigate LC activity and its relationship to upper limb impairments following stroke, and we hypothesize that individuals with stroke will exhibit increased PD on the paretic side. Objective: This preliminary study investigates whether PD dynamics differ between individuals with stroke and controls at rest and during a hand opening task. Methods: Participants (4 stroke, 22 control) were seated in a dimly lit lab, fixating on a central cross to minimize confounding pupillary responses. All participants wore Pupil Core glasses (120 Hz) to record bilateral PD and had EMG electrodes placed on the extensor digitorum communis (EDC).

The task consisted of three phases: rest, preparation (~5 s), and self-initiated maximal hand opening. Baseline PD was measured during rest. Task-evoked PD change was calculated as the peak PD following EMG onset minus the baseline PD. **Results:** In stroke participants, the pupil ipsilateral to the paretic hand was consistently larger than the contralateral pupil at both baseline and during the motor task. This lateralization was not observed in controls. These findings suggest increased asymmetry post-stroke, potentially reflecting altered LC activity and greater NE drive ipsilateral to the paretic limb. **Conclusion:** These preliminary results support the hypothesis that stroke induces lateralized changes in pupil diameter dynamics, potentially due to altered, lateralized LC-NE activity. This may explain the reported increase in motor neuron neuromodulation and the associated impairments on the paretic side. Ongoing data collection from additional stroke participants will help clarify the relationship between this lateralization and motor impairment in the paretic limb.

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## **Poster**

### **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.11/E46

**Topic:** D.03. Stroke

**Support:** isf 1244/22  
bsf 2021248

**Title:** Startreact responses reveal maladaptive reticulospinal activity in post-stroke motor control

**Authors:** A. LORBER-HADDAD<sup>1</sup>, N. GOLDHAMER<sup>3</sup>, T. MIZRAHI<sup>4</sup>, S. HANDELZALTS<sup>2</sup>, \*L. SHMUELOF<sup>1</sup>;

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**Abstract:** Stroke often results in long-term motor impairments, with damage to the corticospinal tract (CST) leading to weakness and poor motor control, and disinhibition of the reticulospinal tract (RST) contributing to spasticity and abnormal synergies. While animal studies suggest that RST hyperexcitability may support motor recovery following CST injury, its functional role in human stroke survivors remains unclear. This study investigated whether increased RST excitability, as indexed by the StartReact effect—a rapid motor response to an auditory startling stimuli—contributes to upper limb motor function post-stroke. We assessed 46 stroke survivors and 37 age-matched controls using clinical motor assessments (Fugl-Meyer Assessment, Action Research Arm Test, grip strength, and Modified Ashworth Scale) and the StartReact paradigm.

Stroke participants exhibited significantly greater StartReact effects than controls, indicating heightened RST excitability. A data-driven stratification approach identified a subgroup of stroke survivors with high StartReact responses. This group demonstrated significantly worse motor outcomes, including lower FMA and ARAT scores, reduced grip strength, and increased spasticity, compared to those with typical StartReact responses. Contrary to the hypothesis that RST hyperexcitability may serve a compensatory role, no evidence was found linking it to functional improvements such as grip strength, even among severely impaired individuals. Additionally, heightened StartReact effects were not observed in wrist extensors, suggesting limited RST involvement in distal out-of-synergy movements. Notably, time since stroke onset did not significantly influence RST excitability or motor outcomes, indicating that RST hyperexcitability may be a stable post-stroke feature. These findings suggest that in humans, RST hyperexcitability is associated with maladaptive motor patterns rather than functional compensation. The StartReact paradigm provides a non-invasive, ecologically valid measure of RST activity, offering insights into brainstem contributions to post-stroke motor control. Future longitudinal and stratified studies are needed to further elucidate the role of RST in recovery and its potential as a therapeutic target.

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## **Poster**

### **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.12/E47

**Topic:** D.03. Stroke

**Support:** NIH Grant R01NS099210  
NIH Grant R01NS112942  
NIH Grant R01HD113270  
NSF CAREER Award # 2145321

**Title:** Early Emergence of Abnormal Muscle Synergies Following Stroke

**Authors:** \*A. KHORASANI<sup>1</sup>, C. GORSKI<sup>2</sup>, R. L. HARVEY<sup>3</sup>, J. ROH<sup>5</sup>, M. W. SLUTZKY<sup>4</sup>;  
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**Abstract:** Stroke frequently disrupts muscle coordination, leading to abnormal muscle synergy patterns—atypical groupings of muscle activations that reflect altered motor control and underlying neural mechanisms. In our previous study, we have documented systematic alterations in upper limb muscle synergy structure, particularly in deltoid synergies (Roh et al., 2013). However, the progression of these changes from the acute to chronic phase remains poorly understood. Our goal was to determine when abnormal synergies emerge following

stroke. Electromyography (EMG) was recorded from nine upper-limb muscles—brachioradialis, biceps brachii, triceps (long and lateral heads), anterior, middle, and posterior deltoid, pectoralis major, and trapezius—during point-to-point reaching tasks performed by three groups: the unaffected arm of chronic stroke participants (N=10), chronic stroke participants (N=41), and acute stroke participants (N=21). EMG signals were sampled at 2 kHz, bandpass filtered (50-450 Hz), rectified, and low-pass filtered at 5 Hz. Non-negative matrix factorization was applied to identify muscle synergies, with the number of synergies capped at three per group when the variance accounted for exceeded 90%. Motor impairment was assessed using the Fugl-Meyer Assessment (FMA), and synergy similarity between groups was quantified via dot product similarity. On average, acute patients were evaluated at  $10 \pm 5$  days (mean  $\pm$  SD) post-stroke, while chronic patients were evaluated at  $5.5 \pm 4.6$  years post-stroke. The average FMA score was 15 for acute patients and 16 for chronic patients, indicating similar levels of motor impairment. In the unaffected arm, three dominant synergies were identified: (1) elbow flexor synergy (brachioradialis and biceps), (2) elbow extensor/shoulder abductor synergy (triceps, medial, and posterior deltoids), and (3) shoulder flexor/adductor synergy (anterior deltoid and pectoralis). In both acute and chronic stroke groups, the elbow flexor synergy was largely preserved, but the other two synergies exhibited substantial reorganization, particularly involving the deltoids. A distinct deltoid-dominant synergy, characterized by abnormal co-activation between the anterior and posterior deltoids, was consistently observed in both stroke groups but was absent in the unaffected arm. The presence of similar synergy disruptions across stroke stages suggests that these abnormalities emerge early post-stroke. These findings highlight the importance of early detection of maladaptive synergies and the need for targeted rehabilitation strategies to address these patterns and support motor recovery.

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## **Poster**

### **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.13/E48

**Topic:** D.04. Brain Injury and Trauma

**Title:** Single Nucleus Sequencing and SpinalTRAQ Cervical Cord Mapping of Corticospinal Targets Denervated after Motor Cortex Injury

**Authors:** \*M. KENWOOD<sup>1</sup>, D. BETZ<sup>2</sup>, J. KAISER<sup>3</sup>, A. NAWABY<sup>4</sup>, A. UMANZOR<sup>5</sup>, M. UENO<sup>7</sup>, V. V. SAHNI<sup>8</sup>, D. M. RAMIREZ<sup>6</sup>, M. P. GOLDBERG<sup>9</sup>;

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Res. Institute, Niigata Univ., Niigata, Japan; <sup>8</sup>Burke Neurolog. Inst., Weill Cornell Med., White Plains, NY; <sup>9</sup>Neurol., Univ. of Texas Hlth. Sci. Center, San Antonio, Shavano Park, TX

**Abstract:** Stroke leaves many patients with significant motor impairment. Sprouting of the contralesional corticospinal tract (cCST) into the injured spinal hemicord is associated with improved motor recovery after unilateral primary motor cortex stroke. Utilizing CST anterograde transsynaptic AAV injection in Sun1-GFP mice, time-series single nucleus RNA sequencing, serial two-photon tomography (STPT) of whole cervical cords, and automated registration and quantification via SpinalTRAQ, we hypothesized that post-stroke CST neuronal targets denervated from motor cortex stroke respond by reactivating CST targeting molecules to be reinnervated by the cCST. We injected AAV1-cre into M1 4 weeks prior to induction of a photothrombotic motor cortex stroke or sham surgery (n=2-6 per group) in 8-10 week old male Sun1-sfGFP mice. Nuclei were isolated from the cervical cord from sham mice and at 2, 4, & 6 weeks post stroke and FACS sorted for GFP+ nuclei and sequenced via a Parse Mini kit. Additionally, a cohort of male and female Sun1-GFP mice were subjected to photothrombotic stroke or sham surgery (n = 6 per group) followed 6 weeks later by a contralesional M1 AAV1-cre injection to label reinnervated neurons in the denervated cord. Cervical cords were isolated and processed and quantified via SpinalTRAQ. We characterized the transcriptional responses of CST neuronal targets, specifically the proportionally higher inhibitory neurons, after unilateral cortical denervation as well as the anatomical location, and neurotransmitter class, of spinal neurons with reinnervated by the cCST 6 weeks post-stroke. Reinnervation of phenotypically appropriate spinal interneurons by the contralesional motor cortex may contribute to functional recovery after motor cortex stroke.

**Disclosures:** M. Kenwood: None. D. Betz: None. J. Kaiser: None. A. Nawaby: None. A. Umanzor: None. M. Ueno: None. V.V. Sahni: None. D.M. Ramirez: None. M.P. Goldberg: None.

## **Poster**

### **PSTR214: Stroke: Neuroinflammation and Genetic Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR214.14/E49

**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH/NINDS NS112256  
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

**Title:** Fabp5 is a key regulator of pericyte migration and fibrosis after stroke

**Authors:** \*I. HWANG, J. GARCIA, S. CARMICHAEL;  
UCLA, Los Angeles, CA

**Abstract:** Stroke is a leading cause of mortality and long-term disability worldwide with subsequent scar formation. The process of scar formation is highlighted by excess deposition of

extracellular matrix proteins which blocks tissue repair and prevents functional recovery in brain. However, the cellular and molecular mechanisms underlying fibrotic scar development remain poorly understood. Pericytes, a heterogeneous population of mural cells embedded within the vascular basement membrane, have emerged as key contributors to post-stroke fibrosis. To investigate pericyte-mediated fibrotic responses, we performed single-cell RNA sequencing (scRNA-seq) on *Tbx18-CreERT2 ;tdTomato* mice, profiling pericyte-lineage cells from sham, peri-infarct, and infarct core regions at 7 days post-stroke. In pathway enrichment analysis, we found that up-regulated genes revealed a strong association with cell migration. Notably, Fatty Acid Binding Protein 5 (Fabp5), a lipid transporter involved in cellular metabolism, migration, and inflammation, was the most highly upregulated gene in activated pericytes. To validate Fabp5 expression in vivo, we performed fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC) at multiple time points as sham, 3, 7, and 14 days post-stroke. Fabp5 expression peaked at 7 days post-stroke and declined thereafter. In parallel, using two-photon microscopy in *Tbx18-CreERT2;tdTomato* mice, we observed that pericyte migration into the infarct core occurred primarily between days 3 and 7 post-stroke. To examine its functional role, we administered a Fabp5 inhibitor into the lateral ventricle via osmotic mini-pump from day 3 to day 10 post-stroke. We stained the samples and found that Fabp5 inhibition led to a marked reduction in fibrotic scar formation and fewer pericytes migrating into the infarct core. Moreover, we found that inhibition also prevented pericyte detachment from endothelial cells, preserving pericyte-endothelial interactions and reducing the transition of pericytes into ECM-producing cells. These findings suggest that Fabp5 promotes pericyte detachment and migration into the ischemic core, contributing to fibrotic scarring. Pharmacological inhibition of Fabp5 attenuates these effects and represents a potential therapeutic strategy to limit fibrosis and enhance recovery following stroke.

**Disclosures:** I. Hwang: None. J. Garcia: None. S. Carmichael: None.

## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.01/E50

**Topic:** D.03. Stroke

**Support:** UH PFF funding

**Title:** Targeted Mediolateral Platform Shifts Induce Adaptive Use of the Paretic Leg During Gait in Stroke

**Authors:** H. PARK<sup>1</sup>, B.-C. LEE<sup>1</sup>, D. SAYENKO<sup>2</sup>, S. LI<sup>3</sup>, \*S. PARK<sup>1</sup>;

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**Abstract:** Individuals post-stroke often underutilize their paretic leg, relying instead on the non-paretic side, which leads to asymmetric gait and impaired locomotor function. Enhancing engagement of the paretic leg while reducing dependence on the non-paretic leg remains a significant challenge in post-stroke gait rehabilitation. This study investigated whether mediolateral (ML) postural perturbations—applied by mechanically translating the treadmill platform medially during the stance phase of the paretic leg—can promote greater paretic leg use during walking. Thirteen individuals with chronic stroke participated in two randomized, cross-over treadmill walking sessions: one with ML perturbations and one without. Each session lasted 11 minutes (1-min baseline, 8-min adaptation, and 2-min post-adaptation). Walking with ML perturbations resulted in significantly greater increases in the maximum center of pressure toward the paretic side immediately after adaptation (early post-adaptation;  $P = 0.008$ ), with retention observed during the late post-adaptation phase ( $P = 0.01$ ), compared to the control condition. Although paretic hip abductor and adductor muscle activation changes were similar between conditions immediately after adaptation ( $P \geq 0.20$ ), significantly greater activation was observed in the ML perturbation condition during the late post-adaptation period ( $P \leq 0.03$ ). These findings suggest that ML postural perturbations enhance lateral weight shifting toward the paretic limb and promote its active use. This perturbation-based intervention represents a promising strategy for improving paretic leg motor control and restoring gait symmetry in individuals post-stroke.

**Disclosures:** H. Park: None. B. Lee: None. D. Sayenko: None. S. Li: None. S. Park: None.

## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.02/E51

**Topic:** D.03. Stroke

**Support:** NIH R21 HD079584

**Title:** Neural Mechanisms Underlying Gamified Audiovisual Gait Biofeedback During Stepping Practice

**Authors:** \*B. L. ALTERMAN<sup>1</sup>, A. SLUSARENKO<sup>2</sup>, J. L. MIRDAMADI<sup>2</sup>, M. R. BORICH<sup>3</sup>, T. M. KESAR<sup>4</sup>;

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<sup>3</sup>Emory Univ., Atlanta, GA

**Abstract:** A majority of stroke survivors have residual gait deficits even after discharge from rehabilitation. Real-time biofeedback is a promising solution that can enhance the efficacy of gait retraining by promoting motor learning of improved gait patterns. Previously, we showed that gait biofeedback enhances biomechanical variables in the targeted/paretic leg in able-bodied individuals and participants with chronic stroke using a conventional biofeedback interface.

Recently, we designed and implemented a novel gamified gait biofeedback interface to facilitate greater engagement, motivation, and salience during stepping practice. The objective of this work was to compare the neural processes underlying walking without biofeedback (noBF) versus walking with gamified gait biofeedback (ggBF) in a repeated-measures study design to identify potential biomarkers of cortical engagement that are modulated as a function of gait training and performance. Alpha rhythm desynchronization has been observed during sensorimotor stimulation and may be modulated during sensory predictions of upcoming motor execution, and has been validated as an indicator of neuroplasticity in learning. We predict corticomotor excitability and cortical activation are valuable neurophysiological biomarkers modulated during biofeedback-based stepping practice, and hypothesize that compared to noBF, ggBF would induce: (1) larger increases in corticospinal excitability; (2) greater sensorimotor alpha band activation changes. Transcranial magnetic stimulation was delivered to the left primary motor cortex, and motor-evoked potentials (MEPs) were recorded from the right soleus muscle before and after 12-minute stepping practice bouts without (noBF) and with biofeedback (ggBF). We used electroencephalography (EEG) to obtain quantitative cortical activation data during each treadmill walking bout. Data have been collected on 2 able-bodied adults (1 male; age =  $27.5 \pm 4.9$  years; planned N = 15). Preliminary results show that compared to noBF (0.14 mV & -0.27 mV), ggBF induced a larger change in MEP amplitude (0.25 mV & 0.39 mV) from pre- to post-walking practice, indicating greater increase in corticomotor excitability following ggBF. During ggBF, we observed increases in EEG alpha power in the parietal cortices bilaterally, and decreases in EEG alpha power in the frontal cortices bilaterally. These results suggest it is feasible to collect cortical activity data using EEG during treadmill walking with ggBF. Our work lays foundations for examination of how ggBF may promote greater motor learning and neuroplasticity during gait retraining.

**Disclosures:** B.L. Alterman: None. A. Slusarenko: None. J.L. Mirdamadi: None. M.R. Borich: None. T.M. Kesar: None.

## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.03/E52

**Topic:** D.03. Stroke

**Support:** RS-2021-KD000003  
RS-2023-00248118

**Title:** Appropriate Candidate for a Torque-assisted Exoskeletal Wearable Robot in Stroke Patients

**Authors:** \*W. CHANG<sup>1</sup>, H.-B. CHOI<sup>1</sup>, T.-W. KIM<sup>2</sup>;

<sup>1</sup>Samsung Med. Ctr., Seoul, Korea, Republic of; <sup>2</sup>Rehabil. Med., Seoul Natl. Univ., Yangpyeong-gun, Korea, Republic of

**Abstract: Introduction:** Wearable exoskeletal robots have emerged as a promising solution, offering dynamic, adaptive assistance to improve walking function. However, the optimal patient profile for benefiting from such devices remains unclear. This study aimed to identify appropriate candidates for torque-assisted exoskeletal wearable robots among subacute stroke patients by analyzing immediate ambulatory effects and related clinical factors. **Methods:** A subgroup analysis was conducted using data from an international, multicenter, randomized controlled trial comparing robot-assisted gait training (RAGT) with conventional gait training in subacute stroke patients. Fifty-five patients who completed four weeks of RAGT were assessed for ambulatory function immediately after training, both with the exoskeleton on and off. Gait was evaluated using the 10-Meter Walk Test, 6-Minute Walk Test, and physiological cost index. Additional assessments included the Functional Ambulatory Category, Fugl-Meyer Assessment-Lower Extremity, Motricity Index-Lower Limb, Trunk Control Test, and Berg Balance Score. Patients were classified as good-responders, no-responders, or poor-responders based on changes in walking performance with exoskeletal assistance, using minimal clinically important difference thresholds. Univariate and multivariate ordinal logistic regression analyses were conducted to identify factors associated with responsiveness. **Results:** Among the 55 patients, 38.2% were classified as good-responders, 12.7% as no-responders, and 49.1% as poor-responders. Good-responders had significantly lower baseline scores in ambulatory function, balance, and lower limb motor function compared to poor-responders. In the good-responder group, exoskeletal assistance led to significant improvements in gait speed, endurance, and efficiency. Conversely, poor-responders experienced worsened ambulation with the device. Multivariate analysis identified lower baseline Functional Ambulatory Category as the independent predictor of a positive response to exoskeletal assistance ( $p < 0.05$ ). **Conclusion:** Torque-assisted exoskeletal wearable robots may benefit subacute stroke patients with low ambulatory function but could impede walking in those already capable of independent ambulation. Careful patient selection based on functional status, particularly baseline ambulatory capacity, is essential for optimal utilization of wearable exoskeletal robots in stroke rehabilitation.

**Disclosures:** W. Chang: None. H. Choi: None. T. Kim: None.

## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.04/E53

**Topic:** D.03. Stroke

**Title:** Premotor cortex stroke volume as a potential marker to aid in treatment strategies for eating actions in acute stroke

**Authors:** \*G. KOYAMA<sup>1</sup>, T. MIZUISHI<sup>2</sup>, H. ARAKAWA<sup>3</sup>;

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**Abstract:** Previous studies have shown that the premotor cortex (PMC) plays a key role in reaching and grasping actions, as well as motor recovery after stroke. However, the relationship between PMC stroke volume and upper limb-related daily activities, particularly eating actions, remains unclear. This retrospective cohort study aimed to investigate the association between the normalized PMC stroke volume and Functional Independence Measure (FIM) eating score. We analyzed seventeen patients ( $n = 17$ ) with acute PMC infarction admitted to our institution between 2019 and 2023. Patients were included regardless of dominant hand, lesion side, sex, or age to ensure a broad sample. We measured the PMC stroke volume and the total PMC volume, manually using MRI images. We defined the normalized PMC stroke volume as the ratio of the PMC stroke volume to the PMC total volume using the ratio method. FIM eating scores were extracted from medical records at approximately four weeks post-stroke. The statistical analysis consisted of four stages to evaluate the relationship between the normalized PMC volume and FIM eating scores: (1) Spearman's rank correlation analysis was conducted to assess whether the relationship was negative; (2) receiver operating characteristic (ROC) curve analysis was used to determine the cutoff value of the normalized PMC volume corresponding to a FIM eating score of  $\geq 5$  or  $\leq 4$ ; (3) we tested for significant differences in FIM eating scores between two groups divided based on the cutoff value using the Mann-Whitney U test; and (4) logistic regression analysis was performed to evaluate the odds ratio of having a FIM eating score  $\leq 4$  when the normalized PMC volume exceeded the cutoff value. As a result, Spearman's correlation showed a negative relationship between the normalized PMC stroke volume and FIM eating scores ( $P = 0.000481$ ). The ROC analysis identified an AUC of 0.843 with a cutoff value of 0.112 (sensitivity 0.857, specificity 0.900). The Mann-Whitney U test demonstrated a significant difference between patients two groups dichotomized by the cutoff value ( $P = 0.000826$ ). Logistic regression revealed that patients with a normalized PMC volume  $> 0.112$  had an odds ratio of 54.0 for having a FIM eating score of  $\leq 4$  ( $P = 0.00821$ ). In conclusion, our findings showed a negative correlation between the normalized PMC stroke volume and FIM eating scores. Additionally, the cutoff value of 0.112 for the normalized PMC stroke volume indicates a likelihood of the FIM eating score dropping to 4 points or below. These findings suggest that the premotor cortex stroke volume has the potential marker to aid in guiding treatment strategies for eating action in acute stroke.

**Disclosures:** G. Koyama: None. T. Mizuishi: None. H. Arakawa: None.

## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.05/E54

**Topic:** D.03. Stroke

**Title:** Space-tic: spasticity evaluation of the elbow and wrist flexors using isokinetic dynamometry in post-stroke patients

**Authors:** \*S. JULLIAND<sup>1,2</sup>, J. GAVEAU<sup>1</sup>, D. LAROCHE<sup>1</sup>, L. RIGLET<sup>2</sup>, C. PAPAXANTHIS<sup>1</sup>;

<sup>1</sup>Univ. Bourgogne Europe, INSERM, CAPS UMR 1093, Dijon, France; <sup>2</sup>Plateforme d'investigation technologique, CHU Dijon, Dijon, France

**Abstract:** *Background:* Spasticity is a common complication following stroke and is most often assessed using the Modified Ashworth Scale (MAS), despite its limited objectivity and reliability. This study introduces a novel isokinetic dynamometry-based method (Score<sub>Ergo</sub>) designed to quantify spasticity in the elbow and wrist flexor muscles, which are frequently affected post-stroke. The method compares patients' torque profiles to a normative dataset from healthy individuals. *Methods:* Twenty-six post-stroke patients ( $65 \pm 15$  years old in late subacute and chronic phases) and twenty-one healthy controls ( $26 \pm 3$  years old) were recruited. Spasticity was assessed using both the MAS and an isokinetic ergometer. Three torque-based metrics were computed: Peak Torque, Work, and Score<sub>Ergo</sub>. Inter- and intra-rater reliability, construct validity (relative to MAS), and feasibility (pain tolerance and evaluation duration) were evaluated over two assessment sessions. *Results:* Score<sub>Ergo</sub> demonstrated excellent intra- and inter-rater reliability at the elbow ( $n = 23$ ;  $ICC \geq 0.96$ ) and good to excellent reliability at the wrist ( $n = 20$ ;  $ICC \geq 0.90$ ). Other dynamometry-based metrics showed good to excellent reliability ( $ICC \geq 0.85$ ). In contrast, MAS displayed only moderate intra- and inter-rater reliability at the elbow ( $k = 0.52$ - $0.58$ ) and moderate intra- to poor inter-rater reliability at the wrist ( $k = 0.31$ - $0.45$ ). Among the dynamometry measures, only Score<sub>Ergo</sub> showed a significant correlation with MAS: at the elbow ( $\tau_b = 0.47$ ,  $p = 0.003$ ) and at the wrist ( $\tau_b = 0.35$ ,  $p = 0.057$ ). Both assessment methods were well tolerated (median pain score  $< 0.6/10$ ). The MAS was quicker to administer (median 2 minutes 05 seconds) than the isokinetic evaluation (median 15 minutes 39 seconds). *Conclusion:* Score<sub>Ergo</sub> offers a reliable, objective alternative to MAS for assessing spasticity in post-stroke patients. By enabling direct comparison with normative data and quantifying the amplitude of spasticity apparition, it supports more precise and individualized rehabilitation strategies.

**Disclosures:** S. Julliard: None. J. Gaveau: None. D. Laroche: None. L. Riglet: None. C. Papaxanthis: None.

## Poster

### PSTR215: Stroke Recovery in Humans

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.06/E55

**Topic:** D.03. Stroke

**Support:** NIH grant: 5R01HD059783-08

**Title:** Ipsilesional arm training improves dexterity in chronic stroke survivors with severe hemiparesis: a randomized controlled trial

**Authors:** \*C. MAENZA<sup>1</sup>, N. KITCHEN<sup>1</sup>, T. MURPHY<sup>2</sup>, C. J. WINSTEIN<sup>3</sup>, R. L. SAINBURG<sup>4,1</sup>;

<sup>1</sup>Neurol., <sup>2</sup>Penn State Col. of Med., Hershey, PA; <sup>3</sup>Div. Biokinesiol/Physical Ther, USC, Los Angeles, CA; <sup>4</sup>Kinesiology & Neurol., Penn State Univ., University Park, PA

**Abstract: Background:** Although motor deficits in the ipsilesional upper limb following stroke are well documented, standard rehabilitation paradigms typically prioritize the paretic (contralesional) limb, often neglecting the less-impaired ipsilesional arm. Emerging evidence suggests that hemisphere-specific motor control mechanisms contribute to ipsilesional impairments, presenting a potential avenue for targeted therapeutic intervention. **Objective:** To evaluate whether hemisphere-specific training of the ipsilesional upper limb improves motor function in individuals with chronic stroke and severe contralesional upper-limb impairment. **Methods:** In this two-site, randomized controlled trial, 53 adults with unilateral middle cerebral artery stroke and severe contralesional upper-limb impairment (Fugl-Meyer Assessment  $\leq 28$ ) completed 15 training sessions over a five-week period. Participants were randomly assigned to receive either Virtual Reality and Manipulation Training (VRMT) targeting the ipsilesional arm or best-practice therapy for the contralesional arm. The primary outcome was ipsilesional manual dexterity, assessed using the Jebsen-Taylor Hand Function Test (JTHFT). Secondary outcomes included the Fugl-Meyer Assessment of motor function and the Barthel Index of activities of daily living. **Results:** Participants in the VRMT group demonstrated an 11% improvement in JTHFT performance compared to the control group (mean difference =  $-5.73$  seconds; 95% CI,  $-9.21$  to  $-2.25$ ;  $P = .0019$ ). Remarkably, these gains were maintained at both 3-week and 6-month follow-up assessments. No significant between-group differences were observed in Fugl-Meyer or Barthel Index scores. **Conclusion:** Targeted, hemisphere-specific training of the ipsilesional upper limb produces sustained improvements in manual dexterity among chronic stroke survivors with severe contralesional paresis. These findings underscore the therapeutic potential of the ipsilesional limb and support its integration into comprehensive post-stroke rehabilitation protocols.

**Disclosures:** C. Maenza: None. N. Kitchen: None. T. Murphy: None. C.J. Winstein: None. R.L. Sainburg: None.

## Poster

### PSTR215: Stroke Recovery in Humans

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.07/E56

**Topic:** D.03. Stroke

**Title:** The Effect of Skating Exercises as High-Intensity Interval Training on Elderly Stroke Patients

**Authors:** \*M. KIM;  
Soonchunhyang Univ., Cheonan-si, Korea, Republic of

**Abstract:** The purpose of this study is to investigate the effects of skating exercises, a form of High-Intensity Interval Training (HIIT) that can be safely performed by elderly patients with minor stroke, on improving cardiorespiratory fitness (CRF) and to compare these effects with Moderate-Intensity Continuous Training (MICT). Participants aged 65 or older with a National Institutes of Health Stroke Scale score of 3 or lower were recruited. This study was designed as a randomized controlled trial, in which the intervention group engaged in skating exercises following HIIT, while the control group underwent MICT based on treadmill exercise. Both groups of participants performed either HIIT or MICT for 20 minutes per day, four times a week, over three months. A total of 34 elderly patients with minor stroke were recruited, with an average age of 70.7 years. For three months, no injuries or adverse cardiovascular or cerebrovascular events were reported among patients undergoing HIIT or MICT. Both the intervention and control groups showed significant increases in measures of aerobic capacity after the intervention. However, the patients in the intervention group exhibited significantly greater improvements in peak oxygen uptake, ventilatory threshold, and peak MET ( $p=0.005$ ,  $p=0.002$ , and  $p=0.024$ , respectively). Additionally, the Berg Balance Scale (BBS) scores and the skeletal muscle mass index showed significantly greater enhancements in the intervention group compared to the control group ( $p=0.032$  and  $p=0.032$ ). In conclusion, skating exercise as HIIT could be a safe and effective cardio exercise method for the elderly who have experienced a minor stroke.



**Disclosures:** M. Kim: None.

## Poster

### PSTR215: Stroke Recovery in Humans

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.08/E57

**Topic:** D.03. Stroke

**Support:** NIH Grant UH3NS100543  
Enspire DBS, Inc.

**Title:** Vigilance-dependent modulation of cortical evoked potentials elicited by dentate nucleus stimulation in chronic post-stroke patients.

**Authors:** \*O. D. ANDERSON<sup>1,4</sup>, D. L. H. HENAO<sup>5</sup>, N. SLOBODIN<sup>6</sup>, A. G. MACHADO<sup>2</sup>, K. B. BAKER<sup>3</sup>;

<sup>1</sup>Neurosciences, <sup>2</sup>Ctr. Neurolog. Restoration, Cleveland Clin., Cleveland, OH; <sup>3</sup>Dept. of Neurosci., Cleveland Clin., Chesterland, OH; <sup>4</sup>Dept. of Neurosciences, Case Western Reserve Univ., Cleveland, OH; <sup>5</sup>Neurosciences, Cleveland Clin. Fndn., Cleveland, OH; <sup>6</sup>Dept. of Neurosciences, Lerner Res. Inst., Cleveland, OH

**Abstract:** The deep cerebellar nuclei are increasingly being explored as potential targets for neuromodulation-based therapies for neurological and psychiatric indications due to their robust, widespread connections with cerebral cortical circuits (Dum & Strick, 2003). As part of our phase I/II trials to enhance motor rehabilitation for individuals with chronic post-stroke motor deficits, participants undergo unilateral deep brain stimulation (DBS) lead implant targeting the dentate nucleus (DN) contralateral to their stroke-affected cerebral hemisphere (Baker et al, 2023). We use low-frequency DBS-cortical evoked potentials (CEPs) to characterize the effect of different contact locations and pulse parameters on cerebral cortical activity as part of an effort to improve therapeutic programming. Here, we report how fluctuations in participant state, or vigilance, can confound these measures, altering CEP component characteristics. Scalp EEG data were recorded continuously as low-frequency (<6Hz) DBS was delivered using the implanted lead. Participants were seated comfortably in a reclined chair and asked to alternately open and close their eyes, with eyes-closed states extended for up to 20 minutes to encourage vigilance changes. EEG data were subsequently divided into 30-second epochs, and sleep staged (Awake, N1, N2, N3, REM) using USleep v1.0 (Perslev, M., Darkner, S., Kempfner, L. et al, 2021). Sleep stage-specific DBS CEPs were created by segregating pulse timing-locked EEG segments by stage and averaging. Comparisons between conditions were made using changes in peak-to-peak amplitude, latency, RMS power, and wavelets. CEP morphology was found to vary significantly across changes in vigilance, marked by amplitude attenuation and latency delays that increased with decreasing vigilance. This drop in cerebellocortical modulatory effect likely reflects thalamic gating or increased cortical/hippocampal inhibitory feedback in the presence of sleep-related, slow-wave oscillations (Torres-Herraez et al, 2022). These results suggest that future closed-loop therapies may wish to consider how changes in vigilance impact real-time



therapy delivery and, if DBS-CEPs are to be used for programming, it is imperative to ensure that the data are not misinterpreted due to unrecognized fluctuations in vigilance.

**Disclosures:** **O.D. anderson:** None. **D.L.H. Henao:** None. **N. Slobodin:** None. **A.G. Machado:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Enspire DBS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Enspire DBS. F. Consulting Fees (e.g., advisory boards); Enspire DBS. **K.B. Baker:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Enspire DBS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Enspire DBS. F. Consulting Fees (e.g., advisory boards); Enspire DBS.

## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.09/E58

**Topic:** D.03. Stroke

**Support:** National Endowment for the Arts Creativity Connects

**Title:** Clinical trial and algorithmic improvements of the Encephalophone auditory brain-computer interface

**Authors:** \***T. A. DEUEL**<sup>1</sup>, S. SHAN<sup>2</sup>;  
<sup>2</sup>Engin., <sup>1</sup>Univ. of Washington, Seattle, WA

**Abstract:** Therapeutic strategies for patients with severe acquired motor disability are relatively limited and show variable efficacy. Innovative technologies such as brain-computer interfaces (BCIs) have been developed recently that might benefit certain types of patients. Here, we tested a previously described auditory BCI, the Encephalophone, which may offer new options to improve quality of life and function. Eleven subjects with acquired moderate to severe motor disability, who had lost their ability to express themselves musically, were enrolled and 10 completed a clinical pilot study of the hands-free Encephalophone brain-computer interface (BCI). Subjects were briefly instructed on the use of the Encephalophone BCI, which uses EEG measured motor imagery to allow users to generate musical notes in real time without requiring movement. Subjects then underwent a pitch-matching task, a measure of accuracy, to attempt to match a given target pitch 3 times within 10 seconds. They were allowed free play, where they could improvise music over a backing track. After 2-3 songs - approximately 10 minutes - of freely improvised playing, subjects repeated the pitch-matching task. There were 3 sessions of testing and free play per subject, within 2 weeks, with at least one day separating sessions. All subjects, on average, improved their pitch-matching accuracy by 15.6 percentage points and increased their number of hits by 58.7% over the 3 sessions, with all subjects scoring accuracy percentages significantly above random probability (19.05%). A subjective self-reporting survey

of ratings of such factors as a feeling of expressing oneself, enjoyment, discomfort, and feeling of control showed a generally favorable response. We suggest that this training approach using an auditory BCI may provide an innovative solution to challenges in recovery from motor disability. After the completion of this clinical trial, we have made improvements to the calibration process, including the ability to choose the electrode pair with the most signal power difference between classification states, as well as the ability to modify signal power thresholds for each note, to improve pitch resolution. We are testing these improvements to determine if the accuracy of the user has increased in comparison to the previous iteration of the calibration algorithm. Future experiments will explore if patients with motor disability - through use of the Encephalophone - can improve their motor impairment, cognitive function, and create new white matter tracts observed via Diffusion Tensor Imaging (DTI) MRI before and after training.

**Disclosures:** T.A. Deuel: None. S. Shan: None.

## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.10/F1

**Topic:** D.03. Stroke

**Support:** UH3NS100543  
Enspire DBS, Inc

**Title:** Time-frequency and spatial characterization of cortical evoked potentials to cerebellar DN-DBS in post-stroke patients

**Authors:** \*D. L. HENAO<sup>1</sup>, D. ESCOBAR SANABRIA<sup>2</sup>, K. B. BAKER<sup>3</sup>, A. G. MACHADO<sup>4</sup>;  
<sup>1</sup>Cleveland Clin. Fndn., Cleveland, OH; <sup>2</sup>Biomed. Engin. (Lerner Res. Institute), <sup>3</sup>Dept. of Neurosci., <sup>4</sup>Ctr. Neurolog. Restoration, Cleveland Clin., Cleveland, OH

**Abstract:** Our phase I trial of deep brain stimulation (DBS) targeting the cerebellar dentate nucleus (DN) supported the safety and feasibility of chronically stimulating the ascending cerebellothalamocortical (CTC) pathway and showed promise for enhancing motor rehabilitation in chronic stroke survivors (Baker et al., 2023). Treatment was associated further with evidence of physiological changes across the cortico-cerebellar network, including increased motor-related desynchronization centered over ipsilesional premotor cortex and reduced corticocerebellar coherence (Gopalakrishnan et al., 2024). While these studies have documented clinical outcomes and large-scale cortical reorganization, the direct effects of CTC activation on cerebral cortical activity remain underexplored. Here, we characterize the scalp-electroencephalography (EEG)-derived cortical evoked potentials (CEPs) induced by DN stimulation in trial participants. To this end, we aim to: (1) quantify key temporal features of CEPs, across scalp electrodes; (2) study the spectral composition of CEPs using time-frequency analysis; and (3) map the spatial distribution of these temporal and spectral features to uncover topographical patterns of cortical excitability

and oscillatory engagement. Preliminary findings support a reproducible pattern of CEPs across contralateral frontal and central cortical regions, with individual spectral responses observed in the beta to low gamma range (~17-44 Hz). These spectral signatures fall within frequency bands commonly associated with motor planning and sensorimotor integration. By correlating these neurophysiological features with clinical improvements, such as changes in the Upper Extremity Fugl-Meyer Assessment, this study aims to identify candidate biomarkers of effective neuromodulation. These results may contribute to a deeper understanding of the mechanisms by which DN-DBS supports motor recovery after stroke and facilitate DN-DBS therapeutic programming.

**Disclosures:** **D.L. Henao:** A. Employment/Salary (full or part-time): Cleveland clinic foundation. **D. Escobar Sanabria:** A. Employment/Salary (full or part-time): Cleveland clinic foundation. **K.B. Baker:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Enspire DBS, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Enspire DBS, Inc. F. Consulting Fees (e.g., advisory boards); Enspire DBS, Inc. **A.G. Machado:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Enspire DBS, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Enspire DBS, Inc. F. Consulting Fees (e.g., advisory boards); Enspire DBS, Inc.

## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.11/F2

**Topic:** D.03. Stroke

**Support:** The Research Program funded by Korea Disease Control and Prevention Agency 3300-3334-300-260-00, 2013-E33017-00, 2013E-33017-01, 2013E-33017-02, 2016-E33003-00, 2016-E33003-01, 2016-E33003-02, 2019-E3202-00, 2019-E3202-01, 2019-E3202-02, 2022-11-006

**Title:** How Does C-reactive Protein Affect Motor Function at One Week After Ischemic Stroke? A Mediation Analysis of the KOSCO

**Authors:** \*H. LEE<sup>1</sup>, W. CHANG<sup>2</sup>, J. LEE<sup>3</sup>;

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**Abstract: Background and Objectives** Previous studies have shown elevated baseline C-reactive protein (CRP) is associated with unfavorable long-term functional outcomes in stroke patients, though most research has focused on mortality rather than motor function.

We investigated factors influencing CRP levels following ischemic stroke and examined the mechanisms by which CRP affects motor outcomes measured by the Fugl-Meyer Assessment (FMA). **Methods** We conducted a retrospective analysis of patients enrolled in the Korean Stroke Cohort for Functioning and Rehabilitation (KOSCO) between August 2012 and January 2021. Inclusion criteria were first-ever acute stroke, age  $\geq 19$  years, and symptom onset within 7 days. We excluded hemorrhagic stroke,  $>24$ h hospital arrival time, and  $>1$  week intervention timing. CRP levels were dichotomized using a 1 mg/L cutoff (High CRP  $\geq 1$  mg/L vs. Low CRP  $<1$  mg/L). Propensity score matching (1:1 nearest neighbor) was performed to balance baseline characteristics between groups. Motor outcomes were assessed using FMA scores at 1 week post-stroke. We performed mediation analysis using Baron & Kenny approach with Sobel testing to identify mechanisms by which CRP influences motor outcomes. **Results** Among 3,889 ischemic stroke patients analyzed, factors associated with elevated CRP levels included older age, male sex, lower BMI, chronic respiratory disease, congestive heart failure, myocardial infarction, malignant solid tumor, and hypertension. After propensity score matching, patients with high CRP showed significantly lower FMA scores at 1 week compared to low CRP patients: upper extremity ( $46.17 \pm 25.35$  vs.  $53.59 \pm 21.81$ ), lower extremity ( $24.83 \pm 11.56$  vs.  $28.32 \pm 9.83$ ), and total motor function ( $56.19 \pm 34.74$  vs.  $59.28 \pm 33.43$ ). Mediation analysis revealed that the relationship between high CRP and poor motor outcomes was significantly mediated by post-stroke pneumonia, fever during 12-24 hours and 24-72 hours after stroke onset, and recurrence of ischemic stroke (Sobel test:  $p < 0.05$ ). **Conclusions** Elevated CRP levels in the acute phase of ischemic stroke predict worse motor function at 1 week across all motor domains. The adverse effects are mediated through post-stroke pneumonia, acute-phase fever, and stroke recurrence. These findings suggest CRP may serve as an early biomarker for identifying stroke patients at risk for poor motor function, potentially guiding targeted interventions including infection prevention and fever management.

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## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.12/F3

**Topic:** D.03. Stroke

**Support:** Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation

**Title:** Hematoma Aspiration Restores Mitochondrial Function, Reprograms Microglial Metabolism, and Reduces Neuroinflammation in Severe Intracerebral Hemorrhage

**Authors:** \*C.-Y. PANG<sup>1</sup>, H.-K. LIEW<sup>2</sup>, H.-Y. HUANG<sup>4</sup>, S.-T. TSAI<sup>3</sup>, K.-Y. TSENG<sup>5</sup>, M. T. AIRAVAARA<sup>6</sup>, W. HU<sup>7</sup>;

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**Abstract:** Severe intracerebral hemorrhage (ICH) causes extensive hematoma formation, resulting in brain compression, increased intracranial pressure, midline shift, herniation, and high mortality. Although emergent surgical evacuation can alleviate the physical pressure caused by ICH, it has not consistently demonstrated improvements in patient outcomes. This highlights the necessity for clinically relevant models to investigate its potential mechanistic benefits, particularly in relation to mitochondrial restoration and microglial function. We established a rat model of severe ICH via intra-striatal injection of 0.6 U collagenase in 3 µL saline over 15 minutes. Hematoma aspiration was performed 6 hours post-induction, removing approximately 75% of the clot. Neurological outcomes, hematoma volume, mortality, oxidative stress, ATP levels, mitochondrial homeostasis, and neuroinflammation were assessed. Additionally, RNA sequencing and metabolomic profiling were conducted to examine microglial gene expression and metabolic reprogramming post-aspiration. Hematoma aspiration significantly reduced hematoma volume, prevented mortality, and improved neurological function. It also restored mitochondrial integrity by increasing ATP levels, reducing oxidative stress, enhancing mitochondrial biogenesis, and regulating mitophagy. Moreover, aspiration attenuated neuroinflammatory markers (iNOS, MMP9, MPO). Transcriptomic and metabolomic analyses revealed a shift toward a neuroprotective microglial phenotype, characterized by restored homeostatic gene expression and activation of Trem2-dependent DAM stage 2 markers. Metabolic pathways including the TCA cycle, butanoate, alanine, aspartate, and glutamate metabolism were significantly upregulated. Therapeutic hematoma aspiration helps mitigate severe ICH injury by restoring mitochondrial function, reprogramming microglial metabolism, and reducing neuroinflammation, which collectively improve neurological outcomes. These findings provide mechanistic insights into hematoma evacuation and underscore its potential in treating severe ICH.

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## **Poster**

### **PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.13/F4

**Topic:** D.03. Stroke

**Support:** MOST 111-2314-B-303-029-  
MOST 110-2314-B-202-018-

**Title:** Hematoma Aspiration Mitigates ER Stress and Microglial Polarization in Severe Intracerebral Hemorrhage Injury

**Authors:** \*W. HU<sup>1</sup>, C.-Y. PANG<sup>2</sup>, H.-K. LIEW<sup>3</sup>;

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**Abstract:** Objective: Intracerebral hemorrhage (ICH) is a devastating form of stroke characterized by the accumulation of blood within the brain parenchyma, resulting in elevated intracranial pressure, neuronal injury, and high rates of morbidity and mortality. Following hemorrhage, blood-derived components such as hemoglobin and heme trigger endoplasmic reticulum (ER) stress in both neurons and glial cells. Prolonged ER stress activates the unfolded protein response (UPR), leading to cellular apoptosis and exacerbated neuroinflammation. Concurrently, microglial activation plays a pivotal role in the inflammatory response post-ICH. Activated microglia polarize toward either a pro-inflammatory M1 phenotype, which exacerbates injury, or an anti-inflammatory M2 phenotype, which promotes repair. The balance between these phenotypes is crucial for determining disease progression and recovery. Clinically, hematoma aspiration—a surgical procedure to remove accumulated intracerebral blood—is commonly employed to reduce secondary brain injury. This study aimed to investigate the effects of hematoma aspiration on ER stress and microglial polarization in a severe ICH rat model. Method and Material: Severe ICH was induced in rats by intra-striatal injection of 0.6 U collagenase in 3  $\mu$ L sterile saline. Six hours post-induction, approximately 75% of the hematoma volume was aspirated. Transcriptomic changes related to ER stress and microglial polarization were analyzed using RNA sequencing (RNA-seq). Result: Severe ICH significantly decreased expression of the ER chaperone GRP78 and upregulated the pro-apoptotic factor CHOP, indicating heightened ER stress. Hematoma aspiration markedly restored GRP78 expression, reduced CHOP levels, and alleviated ER stress. Additionally, ICH promoted microglial polarization toward the M1 phenotype, as evidenced by increased expression of pro-inflammatory cytokines. In contrast, hematoma aspiration facilitated a shift toward the M2 phenotype, thereby reducing neuroinflammation and improving neurological function. Conclusion: Hematoma aspiration effectively mitigates ER stress and modulates microglial polarization, offering neuroprotective benefits in the context of severe ICH. These findings highlight its therapeutic potential in improving outcomes following hemorrhagic stroke.

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**Poster**

**PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR215.14/F5

**Topic:** D.03. Stroke

**Support:** Veterans Health Administration grant #1I01RX003511-01A2

**Title:** The role of functional connectivity within the non-primary motor network in reaching performance and neuromodulation outcomes after subcortical stroke

**Authors:** \*G. HADDADSHARGH<sup>1,5</sup>, R. DE FREITAS<sup>2,5</sup>, F. LIU<sup>5,6</sup>, A. BOOS<sup>3,5,6</sup>, J. MAK<sup>1,5</sup>, X. FANG<sup>3,5</sup>, G. F. WITTENBERG<sup>3,1,5,4,6</sup>;

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**Abstract:** Internal capsule (IC) stroke can disrupt goal-directed motor function by damaging both the corticospinal tract and broader cortical networks. While primary motor cortex (M1) is often the focus in movement planning and control, non-primary regions such as dorsal and ventral premotor cortex (PMd, PMv) and posterior parietal cortex (PPC) play critical roles. Understanding how resting-state connectivity within these regions relates to motor performance after stroke could guide individualized neuromodulation strategies. We collected resting-state fMRI from 22 neurologically intact adults and 15 individuals with chronic IC stroke. Connectivity analysis focused on eight bilateral regions of interest (PMd, PMv, PPC, and M1), defined and analyzed using the CONN toolbox. In a separate session, participants completed a visually guided reaching task using the KINARM robot while receiving transcranial magnetic stimulation (TMS) to bilateral PMd, PMv, PPC, or the postcentral sulcus (PCS), included as a control site, at subthreshold (80% resting motor threshold), suprathreshold (120%), or no stimulation intensities. In the control group, we used Partial Least Squares (PLS) regression to model the multivariate relationships between resting-state connectivity and individual differences in five kinematic measures across TMS conditions. ROI-to-ROI analysis demonstrated 9 significant clusters in the control group and 6 in the stroke group. Stroke participants showed increased interhemispheric PPC connectivity and reduced connectivity between parietal and premotor regions. In the no-stimulation condition, PLS showed non-significant trends suggesting that stronger bilateral M1 and weaker PPC connectivity may support better performance. In contrast, when subthreshold TMS was applied to ipsilateral PMd there was a significant connectivity model ( $p = 0.034$ ) that explained 28% of the variance in behavior. Individuals with stronger bilateral M1 and weaker PPC connectivity showed more pronounced disruption in spatial accuracy, indicating differential susceptibility to modulation. These findings show that resting-state connectivity patterns can predict both motor performance and sensitivity to TMS. The selective effect of subthreshold stimulation to ipsilateral PMd highlights how individual network architecture influences response. Given the altered bilateral PPC connectivity and disrupted PPC-premotor interactions observed in stroke, PPC may be a promising target for facilitatory TMS. Incorporating the connectivity markers into stimulation may improve the precision and effectiveness of motor rehabilitation strategies.

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**Poster**

**PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.15/F6

**Topic:** D.03. Stroke

**Support:** R01NS127156

**Title:** Mapping of slow tissue dynamics in the cerebral cortex during ischemic stroke using laser speckle contrast imaging

**Authors:** \*E. A. LONG<sup>1,2</sup>, B. LIU<sup>2</sup>, R. P. TANG<sup>2</sup>, J. JIANG<sup>2</sup>, E. ERDENER<sup>3</sup>, M. SIMKULET<sup>2</sup>, P. BRESSAN<sup>2</sup>, D. A. BOAS<sup>2</sup>, X. CHENG<sup>2</sup>;

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**Abstract:** Ischemic stroke occurs when cerebral blood flow is occluded in regions of the brain, triggering a cascade of cell damage and death which manifests in cognitive and behavioral impairments. While it is standard to monitor blood flow dynamics in experimental models of stroke, there is limited understanding of the evolution of cellular dynamics due to a lack of *in vivo* imaging methods. Therefore, a tool that enables simultaneous, wide-field, and longitudinal monitoring of both cerebrovascular and cellular dynamics *in vivo* is needed to study the complex evolution and recovery from stroke. In this study, we have developed an epi-illumination laser speckle contrast imaging (LSCI) system, capable of mapping both blood flow and cellular dynamics using fast and slow speckle dynamics, respectively. While LSCI is typically used to image blood flow, our configured system also measures slower dynamics in the brain tissue. We applied this system to image the spatial and temporal characteristics of the slow tissue dynamics following different stroke models in mice. In mice with permanent distal middle cerebral artery occlusion, the cellular dynamics temporarily slowed in the region containing the stroke core, which returned to pre-stroke values within 3 hours of initiating the stroke, despite blood flow remaining low. This indicates successful decoupling of the signal from conventional blood flow measurements and highlights the potentially additional information provided by monitoring cellular dynamics post stroke. In a group of mice with transient occlusions, blood flow was re-perfused within 90 minutes of initiating the occlusion. In this case, the region of slowed cellular dynamics remained up to 5 hours after stroke initiation despite the restoration of blood flow, and this region coincided with the stroke core at day 2. These results reveal an imaging biomarker associated with cellular damage after stroke which can be measured with LSCI and exhibits distinct spatial and temporal dynamics from blood flow. The characterization and imaging of cellular dynamics *in vivo* can provide additional information about stroke evolution, the spontaneous recovery of tissue, and the evaluation of neuroprotective stroke treatments.

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**Poster**

**PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H



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**Program #/Poster #:** PSTR215.16/F7

**Topic:** D.03. Stroke

**Support:** NINDS Grant R01NS127156  
NINDS Grant T32NS136080  
NIGMS Grant T32GM145455

**Title:** Neurogenic low frequency blood flow oscillations and microcirculatory perfusion associated with stroke recovery

**Authors:** \***R. P. TANG**<sup>1</sup>, E. A. LONG<sup>2</sup>, P. R. BRESSAN<sup>2</sup>, M. G. SIMKULET<sup>1</sup>, K. KILIÇ<sup>1</sup>, G. KÜRELI<sup>3,1</sup>, J. JIANG<sup>1</sup>, E. ERDENER<sup>3,1</sup>, M. THUNEMANN<sup>1</sup>, A. DEVOR<sup>1</sup>, D. A. BOAS<sup>1</sup>;  
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**Abstract:** Focal cerebral ischemia occurs when a thrombus or embolus blocks arterial blood flow, cutting off supply of oxygen and nutrients to the cerebrum and forming a necrotic core of the injury. Recovery after the injury is complex and highly variable, involving vascular and cellular activity and remodeling over weeks to months post-stroke. Low frequency (0.01 and 0.1 Hz) oscillations in vascular signals are one of such activities implicated in stroke recovery, which are known to modulate cortical perfusion and glymphatic flow in different brain states sans disease. Importantly, these oscillations increase across both hemispheres in the acute phase after ischemic stroke, and the strength of these oscillations is predictive of better subsequent behavioral outcome in mice. In this study, we investigated the relationship between low frequency vascular oscillations and behavioral recovery in a mouse model of ischemic stroke. First, we measured low frequency oscillations in blood flow using laser speckle contrast imaging (LSCI) before, during and after photothrombosis. As expected, higher amplitudes of oscillations 1 week after stroke were associated with better behavioral outcome at 2 weeks. Next, we measured capillary stalling in the peri-infarct microcirculation using optical coherence tomography (OCT) simultaneously with LSCI. Higher amplitudes of oscillations were also associated with less capillary stalling at 2 days post-stroke, and less capillary stalling was associated with better behavioral recovery. Finally, in a small number of electrode-implanted mice, fluctuations in the gamma band (30-150Hz) of the local field potential (LFP) were generally found to be well-correlated with vascular fluctuations, leading by ~1 second. Up to 1 week after stroke, however, this correlation was decreased in the core and peri-infarct, where there was also a low power of blood flow oscillations. The correlation was maintained in other regions of the cortex. In summary, these results suggest that increased vascular oscillations may affect better behavioral outcome through decreased capillary stalling, and that the post-stroke increase in oscillations may be dependent on neural coupling in the gamma band.

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**Poster**

**PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.17/F8

**Topic:** D.03. Stroke

**Title:** Volumetric ultrasound localization microscopy reveals temporally dependent vascular remodeling in striatal models of acute CNS injury

**Authors:** \*M. SIMKULET<sup>1,2,3</sup>, A. G. ZHOU<sup>2,3</sup>, J. X. JIANG<sup>3</sup>, D. A. BOAS<sup>2,3</sup>, T. M. O'SHEA<sup>2,3</sup>, X. CHENG<sup>2,3</sup>;

<sup>2</sup>Biomed. Engin., <sup>3</sup>Neurophotonics Ctr., <sup>1</sup>Boston Univ., Boston, MA

**Abstract:** The adult mammalian brain exhibits conserved wound healing responses to acute injuries such as stroke or foreign body insertion, but dynamic temporal regulation of these processes after injury or in response to treatment complicates the study of lesion evolution. Intravital ultrasound imaging enables longitudinal monitoring of vascular structure and function in evolving deep striatal lesions inaccessible to conventional optical microscopy. We aimed to adapt novel ultrasound imaging paradigms to temporally track different types of CNS tissue disruption and healing in the deep striatum. To image vascular remodeling at the capillary scale across entire lesion volumes, volumetric transducer arrays must be employed alongside novel super-resolution methods to resolve vessels <100µm. We used a row-column array to perform volumetric ultrasound localization microscopy (ULM) and velocimetry on wild-type P56 mice. After baseline imaging, experimental groups received focal striatal injections of L-NIO, collagenase, or methylcellulose (MC) biomaterial to induce ischemic strokes, hemorrhagic strokes, or foreign body responses. 3D ULM imaging was performed 1 hour and 1, 3, 7 days post injury, capturing both acute and chronic CNS wound healing. 3D ULM images identified characteristic features of injury repair in the ischemic stroke model- transient ischemia at 1 hour and angiogenic remodeling at 7 days post stroke. In the hemorrhagic stroke model, 3D ULM identified permanent loss of vasculature in the lesion core, and limited angiogenic remodeling over time. For MC injections, B-mode imaging tracked tissue volume displaced by the biomaterial, and ULM revealed angiogenic remodeling at the interface. Altogether, our results highlight the capabilities of 3D ULM for tracking acute vascular remodeling after injury in deep CNS tissue regions, as well as potential future applications for temporally evaluating candidate therapies for augmented wound healing.

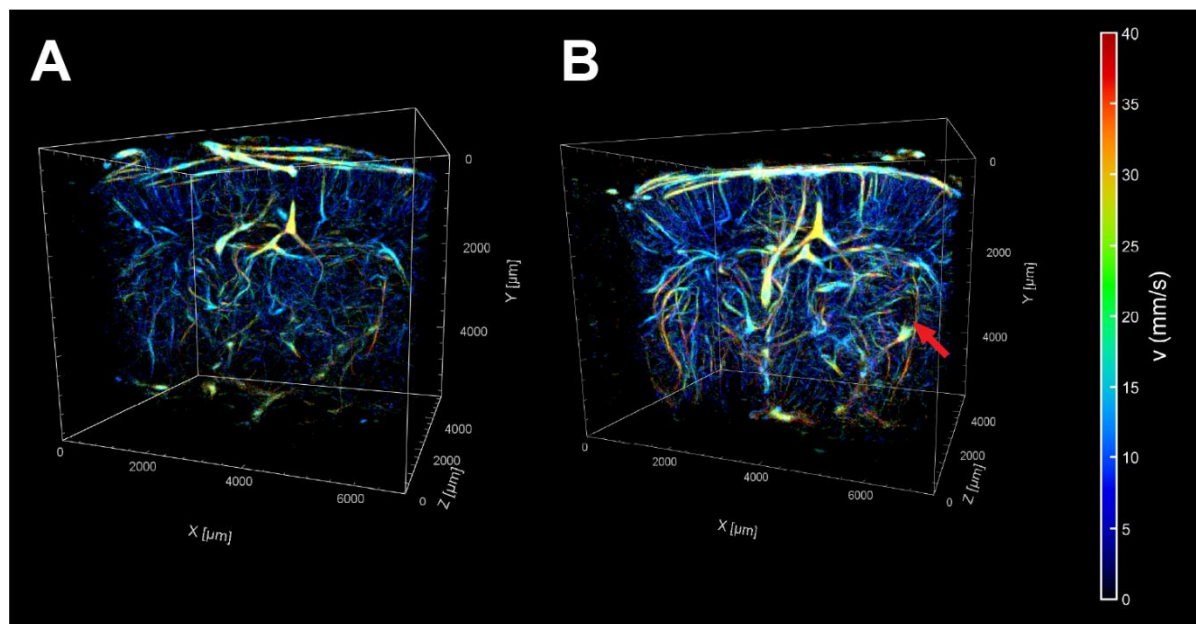


**Figure 1.** 3D ULM velocity maps, mouse brain. *A)* Healthy. *B)* 3 days after ischemic stroke, arrow denotes stroke core.

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## Poster

### PSTR215: Stroke Recovery in Humans

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**Topic:** D.03. Stroke

**Support:** NIH R01 NS115845  
Alzheimer's Drug Discovery Foundation RC-202405-2026586

**Title:** A composite measure of global brain health is associated with motor impairment variability in subacute stroke

**Authors:** \*M. H. KHAN<sup>1,2</sup>, O. MARIN-PARDO<sup>2</sup>, S. CHAKRABORTY<sup>2</sup>, G. BARISANO<sup>4</sup>, M. R. BORICH<sup>5</sup>, S. C. CRAMER<sup>6,7</sup>, J. H. COLE<sup>8</sup>, E. E. FOKAS<sup>9</sup>, N. H. FULLMER<sup>11</sup>, H. KIM<sup>12</sup>, E. R. ROSARIO<sup>11</sup>, H. M. SCHAMBRA<sup>9,10</sup>, N. SCHWEIGHOFER<sup>3</sup>, C. J. WINSTEIN<sup>3</sup>, S.-L. LIEW<sup>2,12,3</sup>;

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Kingdom; <sup>9</sup>Dept. of Neurol., <sup>10</sup>Dept. of Rehabil. Med., NYU Langone Hlth., New York, NY; <sup>11</sup>Res. Inst., Casa Colina Hosp. and Centers for Healthcare, Pomona, CA; <sup>12</sup>Mark and Mary Stevens Neuroimaging and Informatics Inst., Keck Sch. of Medicine, Univ. of Southern California, Los Angeles, CA

**Abstract:** The severity of a stroke's impact on brain structure and function may be influenced by global brain health (GBH), defined here as the cellular, structural, and vascular integrity of the whole brain. Neuroimaging biomarkers such as brain-predicted age difference (brain-PAD), white matter hyperintensity volume (WMH), and perivascular space (PVS) morphology are thought to represent distinct components of GBH (e.g., structural integrity, small vessel pathology, and fluid clearance) and have been individually linked to stroke outcomes. Yet, it remains unclear whether a combined measure of these markers, reflecting overall GBH, also explains stroke outcomes. Here, we hypothesized that a composite baseline GBH score, using principal component analysis (PCA) of brain-PAD, WMH, and PVS, is associated with motor impairment in subacute stroke. We conducted a longitudinal prospective study examining 65 patients from 3 research sites. Behavioral assessment and structural MRI data, including T1-weighted (T1w) and FLAIR acquisitions, were collected within 21 days post-stroke (baseline) and around 90 days post-stroke (follow-up). Brain-PAD was calculated by subtracting chronological age from the predicted age estimated from regional brain features by a publicly available ridge regression model. WMH was obtained using an open-source segmentation tool that integrates T1w and FLAIR inputs. PVS count and average PVS diameter was quantified using a validated method based on T1w morphology and intensity profiles. Stroke lesions were manually segmented using established guidelines to quantify stroke volume and correct segmentation masks. PCA was conducted on baseline brain-PAD, WMH, PVS count, and average PVS diameter. The first principal component (PC1) was then used in a standardized robust linear mixed-effects regression to predict Fugl-Meyer Upper Extremity (FMUE) at follow-up, adjusting for stroke volume, age at baseline, sex, days since stroke onset, days between visits, and intracranial volume, and including a random effect for cohort. PC1 accounted for 35.5% of the total variance across imaging markers. WMH contributed most strongly to PC1 (41.53%), followed by brain-PAD (29.32%) and average PVS diameter (23.68%). Higher PC1 scores predicted lower FMUE scores at both baseline ( $\beta = -0.25$ ,  $p = 0.042$ ) and follow-up ( $\beta = -0.27$ ,  $p = 0.037$ ). We demonstrate that a composite GBH score, derived from brain-PAD, WMH, and PVS metrics, is associated with motor impairment at baseline and 90 days post-stroke. Future work should examine whether other factors influence composite GBH, as this may identify novel therapeutic targets to support recovery after stroke.

**Disclosures:** M.H. Khan: None. O. Marin-Pardo: None. S. Chakraborty: None. G. Barisano: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); G.B. is listed as inventor on a patent application related to this work filed by Stanford University, with no financial interest/conflict.. M.R. Borich: None. S.C. Cramer: None. J.H. Cole: None. E.E. Fokas: None. N.H. Fullmer: None. H. Kim: None. E.R. Rosario: None. H.M. Schambra: None. N. Schweighofer: None. C.J. Winstein: None. S. Liew: None.

**Poster**

**PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.19/F10

**Topic:** D.03. Stroke

**Support:** NIH Grant 2R15HD093086  
Marquette University's Reverend John P. Raynor Endowed Chair Fund

**Title:** The Fugl-Meyer Assessment - Upper Extremity Motor Scale provides insight into spatial efficiency improvements of stroke survivors during extended vibrotactile feedback training

**Authors:** \*R. N. MAZOROW, G. H. GUIDARELLI, K. D. BASSINDALE, R. A. SCHEIDT; Biomed. Engin., Marquette Univ. & Med. Col. of Wisconsin, Milwaukee, WI

**Abstract:** The Fugl-Meyer Assessment - Upper Extremity Motor Scale (FMA-UE) is a widely used measure of motor impairment in post-stroke patients to quantify disease severity and describe motor recovery; scores range from 0 to 66, with higher scores indicating less motor impairment. About half of stroke survivors experience decreased sensation of limb position and movement, leading to decreased upper extremity motor control. Literature suggests that supplemental vibrotactile feedback (VTF) may be a useful compensatory aid to restore functional reach-to-grasp actions. This study examines if baseline FMA-UE scores can predict whether extended training with supplemental VTF can lead to reach-to-grasp improvements on an individual-by-individual basis. We hypothesized that learners of VTF will have higher FMA-UE scores than non-learners under the assumption that greater scores indicate greater capacity to improve kinematic performance. Seven stroke survivors (age:  $65.1 \pm 23.1$  years; FMA-UE:  $48 \pm 10.2$ ) underwent the FMA-UE and 9 hours of training with 3-dimensional VTF informing hand position within peripersonal space during reach-to-grasp actions performed with the contralesional arm; VTF was applied to the stationary ipsilesional arm. The resulting kinematic data were used to compute three primary performance measures: target capture error (a measure of accuracy; Euclidean difference between user's endpoint and target center), average hand speed (a measure of temporal efficiency; user's total distance traveled divided by time), and hand path length ratio (a measure of spatial efficiency; user's total distance traveled divided by optimal path from start to end position). To evaluate changes in kinematic performance, the baseline score from the first session was subtracted from scores obtained after training. Of the seven stroke survivors, three participants significantly improved accuracy, three improved temporal efficiency, and three improved spatial efficiency after training. FMA-UE scores did not differ between learners and non-learners in accuracy and temporal efficiency ( $p > 0.263$ ). However, a significant difference was found for spatial efficiency ( $p = 0.003$ ). Contrary to our hypothesis, participants with lower FMA-UE scores statistically improved their hand path length ratio while using VTF, thereby generating more direct reaches after 9 hours of training. The 95% confidence interval's lower bound for non-learners and upper bound for learners indicates that the FMA-UE threshold between 40.6 and 50.3 may predict whether extended training with VTF can lead to spatial efficiency improvements.

**Disclosures:** R.N. Mazorow: None. G.H. Guidarelli: None. K.D. Bassindale: None. R.A. Scheidt: None.

**Poster**

**PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.20/F11

**Topic:** D.03. Stroke

**Support:** 2 R42 NS098918-02A1

**Title:** Blood plasma samples reflect greater enrichment of neuronal function after stroke

**Authors:** \*K. R. BOOHER;  
Zymo Res. Corp., IRVINE, CA

**Abstract:** Acute ischemic stroke induces widespread cellular necrosis, apoptosis, and activation of inflammation. These mediate release of cell-free DNA (cfDNA) into the circulation. Although increased cfDNA concentrations have been associated with clinical outcome in stroke, data concerning neuronal cfDNA is rare. In this study, we assessed the association of cfDNA with neuron biomarkers in patients with acute ischemic stroke. We recruited an initial cohort of thirteen patients without stroke and nine patients with middle cerebral artery occlusion at the University of Texas Health Sciences Houston-Memorial Hermann Hospital. We collected blood plasma samples and isolated the cell-free nucleic acid material from each subject. The yield of both cfDNA ( $173.2 \pm 207.6$  ng vs  $0.79 \pm 0.48$  ng;  $p=0.037$ ) and cfRNA ( $474.6 \pm 342.3$  ng vs  $59.6 \pm 22.3$  ng;  $p=0.007$ ) was higher in the stroke compared to the non-stroke group. Cell free RNA and whole-genome bisulfite sequencing (miRNA-seq & WGBS) datasets identified significant differences in composition between the two groups, 632 differentially methylated regions (DMRs) & several dozen miRNAs. Gene set analysis found enrichment of pathways for neuronal function, with the top result being “Neuronal System” followed by activity surrounding synapses, demonstrating that a clear enrichment of methylation change in neuronal pathways can be reflected from blood plasma samples following the stroke. Furthermore, cell deconvolution based on DNA methylation patterns showed trends of increased megakaryocyte and oligodendrocytes, which may be involved in the post-stroke inflammatory response. We then recruited a validation cohort made up of 17 stroke and 61 non-stroke volunteers adding whole-proteome analysis to the WGBS and miRNA datasets to confirm our findings. The follow-up cohort once again found significant differences in DNA methylation with enrichment of pathways related to neuronal function. We also found differential expression of miR-190a-5p and miR-9-3p, previously reported as potential biomarkers of stroke recovery, in both cohorts. Proteome analysis found enrichment of viral-mediated immune responses, muscle function impairment, and dysregulated signaling cascades as significantly overrepresented amongst the differentially expressed proteins. Finally, we developed a Random Forest prediction model to predict recovery based on Fugl-Myer scores from a subset of the stroke group. Collectively, the data indicate that blood plasma represents a non-invasive sample source with rich potential for stroke recovery biomarker research and development.

**Disclosures:** **K.R. Booher:** A. Employment/Salary (full or part-time): Zymo Research Corporation.

**Poster**

**PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.21/F12

**Topic:** D.03. Stroke

**Support:** AHA

**Title:** Ischemic stroke induces kidney dysfunction by modulating perfusion dynamics and promoting inflammatory load with age

**Authors:** \***K.-K. MAK**<sup>1</sup>, B. CHELLUBOINA<sup>2</sup>, A. BODA<sup>3</sup>;

<sup>1</sup>Univ. of Illinois Chicago, Chicago, IL; <sup>2</sup>Univ. of Illinois, Chicago, IL; <sup>3</sup>Univ. of illinois chicago, Chicago, IL

**Abstract:** We recently demonstrated the significant influence of renal dysfunction on stroke pathogenesis. We currently evaluated how stroke affects renal function. Adult and aged C57BL/6J mice were subjected to transient middle cerebral artery occlusion (MCAO) for 60 min (adults)/35 min (aged), followed by 24-hour reperfusion to model ischemic stroke. Cerebral blood flow dynamics were assessed using laser speckle at three time points: before ischemia, during ischemia, and post-reperfusion. To assess the renal function dynamically, mice were injected with microbubbles (FUJIFILM) and the kidney function was assessed before being subjected to ischemia, during ischemia, and after reperfusion by Ultrasound. On the first day post-reperfusion, the extent of cerebral infarction was quantified using T2-weighted magnetic resonance imaging. Subsequently, the brain and kidney tissues were collected for molecular analyses. The expression of proinflammatory cytokines and profibrotic markers were measured using a combination of RT-qPCR and transcriptomics profiling. Our investigations showed that stroke significantly reduced renal perfusion. In addition, the expression of profibrotic markers and proinflammatory cytokines were upregulated both in the brain and the kidneys, which suggests a bidirectional pathological communication between the brain and kidneys. In conclusion, our study reports the importance of kidney-brain crosstalk in modulating stroke outcomes. These findings highlight the need to consider renal function not only as a comorbidity, but also as a potential modulator of stroke pathophysiology and therapeutic response especially for interventions requiring renal clearance in old age.

**Disclosures:** **K. Mak:** None. **B. Chelluboina:** None. **A. Boda:** None.

**Poster**

**PSTR215: Stroke Recovery in Humans**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.22/F13

**Topic:** D.03. Stroke

**Support:** 25K14412  
TERUMO lifescience foundation

**Title:** Combinatorial Application of Closed-loop NMES for Periphery and Timing-specific Focal Beta-tACS for Primary Motor Cortex in Post-Stroke Hand Rehabilitation: a double-blind randomized cross-over trial

**Authors:** \*S. TASHIRO<sup>1</sup>, M. TAKEMI<sup>3</sup>, T. TSUJI<sup>4</sup>, S. YAMADA<sup>2</sup>;

<sup>1</sup>Kyorin Univ. Fac. of Med., Tokyo, Japan; <sup>2</sup>Kyorin Univ. Fac. of Med., Mitaka, Japan; <sup>3</sup>Grad. Sch. of Advanced Sci. and Engin., Hiroshima Univ., Hiroshima, Japan; <sup>4</sup>Keio Univ. Sch. of Med., Tokyo, Japan

**Abstract:** Motivation/problem statement: Chronic hand paresis is one of the core and refractory sequelae of stroke that restricts activities of daily living and the quality of life. Although neurorehabilitation utilizing electrical stimulation targeting either the brain or periphery has become common, integrating both approaches remains underexplored owing to the lack of phase I/II studies. Methods/ approach: This double-blind, randomized crossover trial investigated the safety and feasibility of combining transcranial alternating current stimulation (tACS) targeting the cortex with neuromuscular electrical stimulation (NMES) applied to the periphery. The intervention was formed into a one-hour weekly outpatient rehabilitation program, including conventional occupational therapy. The tACS was applied at the primary motor cortex to boost the post-movement beta-rebound following the finger-extension training task assisted by NMES. The precision stimulation principle was incorporated in tACS in terms of the timing of the training task, focality of the montage, individualized frequency of the AC, and in the NMES set to amplify the detected activity of the paretic muscle correctly using a hybrid electrode for detection and stimulation. The result on behavioral and physiological assessments were compared between Real-tACS and Sham-tACS interventions. Results: Ten participants completed ten weekly sessions, and no remarkable adverse events were recorded. After the real-tACS sessions, participants reported less sleepiness ( $p = 0.037$ ,  $r = 0.66$ , t-test), and the weak incrementation of stress measured by heart rate variability ( $p = .010$ ,  $r = 1.19$ , t-test), and the endurance to repeat training tasks, as measured by the transition of detected electromyography, was higher ( $F[1,18] < 2.05$ ,  $p < 0.001$ , repeated-measures ANOVA). Scores of the Fugl-Meyer upper extremity (FMA) and Action Research Arm Test (ARAT) showed enhanced motor recovery in the real-tACS intervention compared to sham (FMA: pre, 27 [19-29.75]; post 30 [22.5-33.75],  $p = .043$ ,  $r = 1.00$ ; ARAT: pre, 6 [4-14.75]; post 8 [5-16.5]). Conclusion/implications: These findings support the safety and feasibility of combining the two modalities of electrical stimulation, tACS and NMES, in stroke rehabilitation, highlighting its potential effectiveness.

**Disclosures:** S. Tashiro: None. M. Takemi: None. T. Tsuji: None. S. Yamada: None.



## Poster

### PSTR215: Stroke Recovery in Humans

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR215.23/F14

**Topic:** D.03. Stroke

**Support:** NIH Grant R21NS120274

**Title:** Speed, but not Accuracy, Arm Movement Training Improves Feedforward Control in Elbow Movements

**Authors:** \*G. HAYRAPETIAN<sup>1</sup>, Y. DARMON<sup>2</sup>, S. KANTAK<sup>5</sup>, E. R. ROSARIO<sup>6</sup>, V. R. BARRADAS<sup>7</sup>, G. E. LOEB<sup>3</sup>, C. J. WINSTEIN<sup>4</sup>, N. SCHWEIGHOFER<sup>8</sup>;

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**Abstract:** Persistent impairments in upper-limb function after stroke indicate that motor control remains insufficiently targeted by conventional rehabilitation. Impaired control of arm movement post-stroke is, at least in part, due to a deficit in feedforward control. However, it is unknown whether feedforward control can be recalibrated with motor practice. Here, we tested feedforward control at the elbow joint ~1 week before and again 3 days and 1 month after multi-joint task training as a part of the FAST clinical trial (Darmon et al., 2025). Participants with mild to moderate impairments (Fugl-Meyer scores: median 44, range 26-57) resulting from chronic stroke underwent intensive whole-arm training over four days in one of two practice conditions groups: speed-focused (N = 19) or accuracy-focused (N = 19) practice conditions. Feedforward control of elbow movement was assessed with a task modified from by Sainburg & Schaefer (2004) using a specially built apparatus that constrained movements to the elbow. Participants performed 60 rapid elbow movements, comprising 10 flexions and 10 extensions at each of three amplitudes: 30°, 50°, and 70°. Initial peak acceleration, which occurs before sensory feedback can influence the movement, served as a proxy for the initial feedforward motor command. Appropriate scaling of initial peak acceleration to movement amplitude reflects robust feedforward control, while reduced scaling indicates poor feedforward control. Across all participants, the less-affected arm exhibited steeper scaling than the more affected arm. At both day 3 and 1-month post-training, the speed group exhibited significantly increased scaling of the more affected arm relative to both their baseline and to the accuracy group. These results support the view that intensive, fast practice can improve a fundamental component of control at the joint level in a task where no compensation is possible, thereby challenging the prevailing view that only compensatory strategies can improve in the chronic stage post-stroke.

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**Poster**

**PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.01/F15

**Topic:** D.04. Brain Injury and Trauma

**Support:** Daisy Brand Undergraduate Research Grant Competitive Program 2025

**Title:** Characterizing CRYAB's binding and oligomerization states in human cerebral organoid models of mTBI

**Authors:** \*E. A. PALACIOS<sup>1</sup>, N. YASIN<sup>2</sup>, Z. R. LYBRAND<sup>3</sup>;  
<sup>1</sup>Biol., Texas Woman's Univ., Denton, TX; <sup>2</sup>Biol., <sup>3</sup>Dept. of Biol., Texas Woman's Univ., Denton, TX

**Abstract:** Mild traumatic brain injury (mTBI) accounts for the majority of head injuries in the United States, characterized by temporary symptoms and steady recovery. However, repeated mTBIs have been linked to neurodegenerative diseases, such as chronic traumatic encephalopathy (CTE), which can result in progressive cognitive decline and lasting neurological damage. To investigate the underlying mechanisms of mTBI, human cerebral organoids were generated to more closely resemble the human physiological response to injury in vitro. Organoids were loaded into a computer-controlled tabletop blast chamber and exposed to 250 kPa at 5000 Hz to inflict a mild injury. Control and blasted organoids were prepared for single cell RNA sequencing. Differential gene expression analysis revealed upregulation of the  $\alpha$ B-crystallin (CRYAB) gene in the blast conditions. Further immunohistochemistry analysis confirmed expression of CRYAB protein in blasted organoids. CRYAB, a molecular chaperone belonging to the small heat shock protein (sHSP) family, binds ubiquitously to prevent misfolding—a key feature of neurodegeneration. Misfolded proteins are more likely to bind to each other and aggregate, but if CRYAB binds to them early enough, it may prevent further misfolding until they can be refolded or marked for degradation. Published studies have provided evidence for a plausible negative correlation between a protein's oligomerization state and its chaperone function. If CRYAB's structural state plays a role in its binding activity, specifically to known pathological client proteins involved in neurodegeneration, this inverse relationship could be key to further understanding its role in the context of mTBI. Six-month-old human cerebral organoids were subjected to hydrostatic blast injury in three experimental groups — control, single (1x), and triple (3x) blast. Lysates have been collected and are currently being used to assess the oligomerization states and binding partners of CRYAB across baseline and injured conditions. These findings may elucidate CRYAB's binding interactions in connection to known neurodegenerative proteins following mechanical trauma, in addition to characterizing and understanding mechanisms involved in mTBI.

**Disclosures:** E.A. Palacios: None. N. Yasin: None. Z.R. Lybrand: None.

**Poster**

**PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.02/F16

**Topic:** D.04. Brain Injury and Trauma

**Title:** Investigating CRYAB's Ser59 phosphorylation in human cerebral organoids following mild traumatic brain injury

**Authors:** \*N. YASIN<sup>1</sup>, Z. R. LYBRAND<sup>2</sup>, E. PALACIOS<sup>3</sup>;

<sup>1</sup>Biol., <sup>2</sup>Dept. of Biol., Texas Woman's Univ., Denton, TX; <sup>3</sup>Texas Woman's Univ., Denton, TX

**Abstract:** In an effort to uncover molecular response to mild traumatic brain injury (mTBI), we identified significant upregulation of the small heat shock protein crystallin alpha B (CRYAB) in human cerebral organoids following a blast exposure. mTBI is the most prevalent form of TBI and is linked to neurodegeneration. CRYAB is implicated in protein homeostasis and cytoprotection in the central nervous system (CNS), but its role in mTBI remains unknown. We utilized a human cerebral organoid model subjected to controlled blast exposure via a table-top blast chamber and investigated CRYAB expression at the protein and transcript levels. Single cell RNA sequencing revealed CRYAB is upregulated 1 hour after blast. Histological analyses demonstrated CRYAB protein expression peaked 24 hours after injury, suggesting a delayed translational response. Western blot analyses confirmed increased CRYAB protein expression. To assess CRYAB's functional role after injury, we are investigating the phosphorylation state of CRYAB at Serine-59, a post translational modification known to modulates its chaperone activity. Preliminary findings suggest that phosphorylation at Serine-59 is increased in injured vs control organoids, but also progressively elevated with repetitive blast exposure. Collectively, our findings suggest that CRYAB is dynamically regulated after mTBI and may play a role in modulating injury progression or recovery.

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**Poster**

**PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.03/G1

**Topic:** D.04. Brain Injury and Trauma

**Support:** Start-up funds to Liaudanskaya at University of Cincinnati

**Title:** Mitochondrial Crisis and Delayed Tauopathy Following Repetitive Mild Brain Injury in a Human 3D Brain Model

**Authors:** \*V. LIAUDANSKAYA;  
Univ. of Cincinnati, Cincinnati, OH

**Abstract:** Chronic traumatic encephalopathy (CTE) is a progressive tauopathy associated with repetitive mild traumatic brain injury (rmTBI), but the early molecular and cellular mechanisms that drive its onset remain poorly defined. Traditional rodent models fail to recapitulate the progressive nature of CTE and the human-specific tau isoform complexity. Here, we use a human 3D in vitro brain tissue model composed of neurons, astrocytes, microglia, and brain microvascular endothelial cells to study the spatiotemporal dynamics of tau pathology following three mild mechanical injuries spaced 14 days apart. Our preliminary data reveal a distinct, biphasic tauopathy progression. In the acute phase (0-72h post-injury), we observed transient membrane instability, suppression of tunneling nanotube (TNT) markers, and a drop in oxidative phosphorylation (OCR), accompanied by elevated extracellular phosphorylated tau (pTau), TDP-43, and neurogranin. This early phase appears dominated by stress-induced passive leakage of pathological proteins, without notable intracellular tau accumulation. By 2 weeks post-injury, TNT and uptake pathway markers such as TNFAIP2 and paxillin returned to baseline or became upregulated, coinciding with a second spike in extracellular pTau and neurodegenerative markers. This suggests a shift from passive leakage to active intercellular propagation. In the chronic phase (4-8 weeks), we observed robust intracellular accumulation of pTau (AT8, PHF1, Thr231), calpain-1 upregulation, and sustained elevation of OCR and  $\alpha$ KG/2HG ratios, indicative of persistent mitochondrial stress and epigenetic remodeling. Cell-type-specific mitochondrial tracing revealed delayed mitochondrial transfer from glial cells to neurons, suggesting that glial cells may propagate dysfunction via intercellular organelle trafficking. Collectively, our findings demonstrate that initial neuronal damage is followed by delayed, maladaptive mitochondrial transfer and tau seeding. These results highlight the importance of glial-neuronal interactions and mitochondrial dynamics in injury-induced tauopathy and offer mechanistic insights into the early drivers of CTE.

**Disclosures:** V. Liaudanskaya: None.

**Poster**

**PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.04/G2

**Topic:** B.08. Epilepsy

**Support:** NIN/NINDS R01NS097750  
R37NS069861  
CIRM (Award # EDUC4- 12752)

**Title:** A Human iPSC-Derived Brain Organoid Model Recapitulates Key Features of Concussive Brain Injury

**Authors:** R. JABERI<sup>1</sup>, \*C. TAITANO-JOHNSON<sup>3</sup>, P. OKORO<sup>2</sup>, I. NOSHADI<sup>2</sup>, V. SANTHAKUMAR<sup>4</sup>;

<sup>1</sup>Mol. Cell and Syst. Biol., <sup>2</sup>Univ. of California Riverside, Riverside, CA; <sup>4</sup>Mol. Cell and Systems Biol., <sup>3</sup>Univ. of California, Riverside, Riverside, CA

**Abstract:** Traumatic brain injury (TBI) is a leading cause of neurological disability, often resulting in long-term cognitive and behavioral deficits. Although rodent models have advanced our understanding of TBI mechanisms, they do not fully capture the molecular complexity of human brain responses. Human induced pluripotent stem cell (iPSC)-derived brain organoids offer a physiologically relevant platform to model human-specific injury responses. However, concussive brain trauma, one of the most prevalent forms of TBI, has yet to be reliably replicated in organoids. To address this gap, we established and characterized a novel TBI model in human brain organoids that recapitulates key features of mild brain injury, providing a platform for studying human-relevant mechanisms of injury and repair. Human forebrain organoids (hFBOs) were generated from SCTi003-A iPSCs using a modified Pasca protocol. These organoids express neural stem cell (NSC) markers including Nestin, Sox2, and ZO-1 at early stages, and exhibit neuronal differentiation with MAP2, GABA, and SST expression by later stages. Whole-cell patch clamp recordings confirmed progressive functional maturation of hFBOs, with high input resistance and limited synaptic activity at day 80, and increased excitability, spontaneous EPSCs, and dendritic complexity by day 150. To model concussive injury, we adapted the Cell Injury Controller II (CICII) to deliver controlled mechanical trauma to hFBOs at mild (1.5 psi), moderate (2.0 psi), and severe (2.5 psi) levels. TUNEL staining revealed stimulus- and time-dependent increases in apoptotic cell death, confirming that the model accurately recapitulates graded injury severity. Functional assessment using Fluo-8 calcium imaging demonstrated heightened calcium transients and abnormal synchronous network bursts in injured organoids, mimicking the hyperexcitability observed in rodent TBI models. Notably, this activity was intensity-dependent and most pronounced following severe injury. Together, these findings validate the hFBO-CICII model as a robust platform for studying human-specific mechanisms of brain injury. This model enables mechanistic dissection of trauma-induced alterations in neurogenesis, excitability, and cell death, and provides a scalable system for testing therapeutic interventions in a human context.

**Keywords:** Traumatic Brain Injury, Brain Organoids, Human iPSC, Calcium Imaging, Cell Death

**Grants:** NIN/NINDS R01NS097750 and R37NS069861 to VS, CIRM (Award # EDUC4-12752)To RJ

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**Poster**

## **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.05/G3

**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH R01NS097549  
NIH U01NS069545  
NIH R01NS039679  
NIH R01NS115994  
Georgia Research Alliance

**Title:** Transcriptional analysis following mild traumatic brain injury reveals distinct correlation profiles in a young brain following high and low rotational loads

**Authors:** \*O. ADERIBIGBE<sup>1</sup>, L. WOOD<sup>2</sup>, S. MARGULIES<sup>1</sup>;

<sup>1</sup>Wallace H. Coulter Dept. of Biomed. Engin., Georgia Inst. of Technol. & Emory Univ., Atlanta, GA; <sup>2</sup>Inst. for Bioengineering and Biosci., Georgia Inst. of Technol., Atlanta, GA

**Abstract:** Traumatic brain injury (TBI) is a leading cause of death and disability in young children. Falling is the most common cause of TBI in young children and can lead to heterogeneous injury severities and outcomes. Additionally, head rotation during falling can amplify injury. However, there is a paucity of data evaluating molecular changes associated with different degrees of rotational loads in pediatric TBI. Because transcriptional profiling gives a holistic view of tissue-level changes, we hypothesized that gene expression associated with worse injury outcome would correlate with higher rotational velocities. To test this, we investigated transcriptional changes in the frontal lobe of newborn anesthetized 3 - 5-day old female Yorkshire piglets exposed to Low ( $47.38 \pm 4.9$  rad/s, N=4) and High ( $149.68 \pm 2.9$  rad/s, N=8) rapid non-impact head rotations (RNR), and shams (N=6). Brains were perfused and collected, 1-day post-injury, then formalin-fixed, paraffin-embedded (FFPE) and processed for RNA-sequencing. Differential expression analysis revealed distinct transcriptional profiles following Low and High RNR. The Low and High RNRs resulted in 780 and 333 differentially expressed genes (DEGs) respectively, with only 91 overlapping DEGs ( $p \leq 0.05$ ,  $|\log_2FC| > 1$ ). DEGs from both groups were consistent with the presence of injury, amyloid beta (A $\beta$ ) accumulation, stress, neurogenesis, and survival. To understand the patterns of DEGs within each group and their relationships with both degrees of angular velocities (rad/s), a spearman correlation (R,  $p \leq 0.05$ ) was conducted. Surprisingly, from the High group, we observed that most upregulated DEGs (*ARK2C*, *RPLP0*, *SMTN*, *GABARAP*) involved in regulating protective functions like autophagy, axonal growth, survival, cytoskeletal maintenance, and inflammation attenuation were positively correlated to angular velocity, while most downregulated DEGs (*FSD1*, *FAM114A2*, *CYB5R4*, *LPL*) involved in increased mitochondrial and neuronal dysfunction were negatively correlated with angular velocity. In contrast, from the Low group, most upregulated DEGs (*PRKN*, *SLITRK2*, *PRDM16*, *TXNRD2*) involved in protective and mitochondrial functions were negatively correlated with angular velocity, while most downregulated DEGs (*MX2*, *ARMC12*, *RNF8*, *HNRNPM*) associated with increased dysfunction

were positively correlated to angular velocity. In total, our data reveal distinct transcriptional profiles between the Low and High RNR groups, with increased growth and protective DEGs in the High group that were not observed in the Low group. These DEGs highlight specific diagnostic targets for injury severity in a young brain.

**Disclosures:** O. Aderibigbe: None. L. Wood: None. S. Margulies: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.06/G4

**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH Grant F31NS135948  
Belfer Neurodegeneration Consortium

**Title:** A single-cell atlas of neurons and glia in the injured American cockroach brain

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**Abstract:** Understanding how the nervous system remodels and recovers in response to injury is crucial for improving therapeutic outcomes for patients suffering from traumatic brain and spinal cord injuries. While mammalian model systems may offer the highest fidelity to human biology, this comes at the expense of greater cost and complexity. Insects are an appealing alternative given their simplified nervous systems and dramatically lower maintenance costs. In particular, the American cockroach (*Periplaneta americana*) is a powerful yet underutilized model for studying nervous system responses to injury. With a large and accessible nervous system, robust olfactory and navigational behaviors, and remarkable resilience to injury, the cockroach is well-suited for investigating mechanisms of neural repair, circuit recovery, and behavioral rehabilitation. Despite these compelling features, prior work with cockroaches has largely been confined to behavioral and systems-level studies as little molecular characterization has yet been performed. To bridge this gap, we applied long read RNA sequencing and single-cell RNA-seq to characterize transcriptomic diversity among both neuronal and glial cell types in the adult cockroach brain. By combining previously published bulk RNA-seq data from peripheral tissues, orthologous protein sequences from related species, and our long read and single-cell RNA-seq data, we create a refined genome annotation which identifies thousands of protein coding genes absent in the current NCBI reference genome annotation. Leveraging this new annotation with our single-cell RNA-seq dataset, we identify cholinergic, GABAergic, glutamatergic, and monoaminergic neuronal subclasses as well several glial cell types, including astrocytes, ensheathing glia, and cortex glia. We further contrast molecular signatures of observed cell populations with those previously identified in fly and mouse. To better understand how the

cockroach nervous system responds to perturbation, we performed single-cell RNA-seq 48 hours following bilateral antennectomy. We find that glia remodel most dramatically following this injury and compare these changes to those observed in reactive gliosis in other insect and mammalian species. This study provides a large atlas characterizing the neuronal and glial cell type diversity of the cockroach brain and revealing dynamic transcriptomic remodeling among multiple cell types in response to acute injury. This work highlights the utility of the American cockroach for investigating neuron-glia interactions following acute trauma, laying the groundwork for future molecular studies in this species.

**Disclosures:** **N.D. Kathman:** None. **M. O'Dea:** None. **S.A. Liddelow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); S.A.L. maintains a financial interest in AstronauTx Ltd. and Synapticure. F. Consulting Fees (e.g., advisory boards); S.A.L. is on the Scientific Advisory Board of the Global BioAccess Fund and the MD Anderson Neurooncology program.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.07/G5

**Topic:** D.04. Brain Injury and Trauma

**Support:** PANTHER award N000142112044  
PANTHER award N000142112855

**Title:** A Novel Microfluidic Traumatic Brain Injury-on-a-Chip Approach for Delineating Cellular Pathologies

**Authors:** \***M. ARAIZA CANIZALES**<sup>1</sup>, G. RADTKE<sup>3</sup>, C. FRANCK<sup>2</sup>;

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**Abstract:** Every year millions of Americans are affected by traumatic brain injury, making it a major public health concern. Broadly, TBI can be classified based on its severity by medical personnel after identifying the patient's response to various stimuli. However, the current state of the field fails to recognize the underlying injury mechanism and their repercussions in the short and long term. Biological pathways leading to TBI are mainly categorized into primary and secondary injury. In the former, the tissue is physically damaged after mechanical loading, resulting in immediate cell death, whereas in the latter cell death is triggered by biochemical processes that take hours to manifest, but can lead to developing neurogenerative disorders. Recent *in vitro* models of TBI have been used to elucidate either of these two injury types, but to date no single platform has provided the means to investigate the transition between them. State-of-the-art mechanical devices are inertially limited and thus are challenged to reach strain rates



beyond the  $200\text{ s}^{-1}$  regimes and into the  $1000\text{ s}^{-1}$ , in particular for ultrasoft, small (order millimeter) biologically active samples. Thus, there is a need for defining a threshold between these two injury types to improve diagnosis and care for TBI patients. In response, we developed a novel microfluidic chip capable of inducing low and high strain rates in the order of 25 to  $1500\text{ s}^{-1}$ . Utilizing this microfluidic device, we compression-shear rat cortical spheroids through a constriction, where the strain and strain rate are solely determined by the fixed geometry of the channel and the fluid flow. To assess the spheroids for the presence of cellular hallmarks of TBI, we performed a viability and neuronal activity assay immediately and 24 hours post mechanical insult. Preliminary results showed a decrease in cell viability 24 hours after injury for both sets of samples, whereas only the high-rate spheroids exhibited reduced viability immediately after insult. Electrical activity followed a similar trend, indicating the presence of primary injury in the high-rate samples.

**Disclosures:** M. Araiza Canizales: None. C. Franck: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.08/G6

**Topic:** D.04. Brain Injury and Trauma

**Support:** ONR N000142112044  
ONR N000142112855  
ONR N000142212828

**Title:** Strain-based cellular injury thresholds in a 3D in vitro model of traumatic brain injury (TBI)

**Authors:** \*J. L. PARK<sup>1</sup>, J. ZHANG<sup>2</sup>, C. FRANCK<sup>2</sup>;

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**Abstract:** Diagnosis and prediction of secondary injury, induced via delayed cellular signaling pathways, after a traumatic brain injury (TBI) has remained elusive. We present a methodology for determining a cellular injury threshold curve as a function of sex, cell phenotype, strain magnitude and strain rate. We dissected and seeded male and female cortical cells from postnatal day P0-P1 Sprague-Dawley rat pups into 3D dogbone shaped scaffolds made from type-I rat tail collagen. After 7 days in vitro, cells were stained with Calcein AM, a live cell indicator and imaged using multiphoton microscopy with a 20x WI objective. Following imaging, samples were stretched in uniaxial tension using an on-scope device that delivers a controlled impact at precise programmed strain magnitudes and rates (Summey, L et al, 2023). After impact, cells were returned to the incubator. 24 hours later, we re-stained cells with Calcein AM, Hoechst (nuclear stain), and EthD-1 (dead cell indicator), and imaged at the same location as the pre-impact image. We traced the stained live cell image in NeuronStudio and ran it through a strain-

mapping MATLAB code to output a single cell with mapped strains along the branches, mean shear, mean compressive and mean tensile strains across the cell, and branch orientation data. We converted the traced neurons to a tree structure in MATLAB and then transformed and mapped the far field strain onto the local cell structures by rotating the far-field strain tensor via a rotation matrix defined by an orthonormal discrete Frenet frame (Scimone, et al., 2018). The average strain each cell experienced was then correlated with post-impact cell fate to generate points on the critical injury threshold curve. Concurrently, we stained and imaged samples with Calcein AM of a negative control sample then fixed samples with 4% v/v paraformaldehyde and 8% w/v sucrose, immunostained for cell phenotype, and imaged at the same location as the live image. We fed both images into an unsupervised machine learning algorithm to identify cells based on morphology alone. Preliminary results indicate that cells with long projections along the x or y axis exhibited cell death 24 hours post-impact. Conversely, cells with shorter projections remained viable despite experiencing comparable strain magnitudes. Impacts occurred at 50 strains/second with a far-field strain magnitude of 30%. We also identified a spatial dependency in cell viability influenced by cell phenotype and quantity of nearby cells. This secondary injury curve holds significant promise for development of new predictive injury metrics, diagnostic criteria, and design of protective equipment to prevent TBI.

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## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR216.09/G7

**Topic:** D.04. Brain Injury and Trauma

**Support:** N000142212828

**Title:** Microglia activation and neuroinflammation following in vitro traumatic brain injury

**Authors:** \*E. BLICK<sup>1</sup>, C. FRANCK<sup>2</sup>, A. HAI<sup>1</sup>;

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**Abstract:** Neuroinflammation after traumatic brain injury (TBI) is an underexplored connection between primary injury and neurodegenerative disease, with post-mortem studies revealing widespread immune activation in the brain up to 18 years post-injury. Microglia, the brain's resident immune cells, play a central role in the aftermath of TBI, as their prolonged activation contributes to secondary injury, cognitive decline, and neuronal death. Highly responsive to their surrounding environment, microglia undergo functional and morphological changes in reaction to inflammatory cues, shifting between pro-inflammatory and anti-inflammatory states. While most studies of microglial activation use lipopolysaccharide (LPS), a bacterial membrane component that engages microglial-specific receptors, research investigating the response of microglia to mechanical impacts is lacking. Furthermore, most TBI studies are conducted *in vivo*

and, although biologically complex, they preclude reliable application of strain with the accuracy required to determine a correlation between impact and inflammatory response at a single cell level. In this study, we employ a novel, reproducible *in vitro* model of TBI to investigate changes in neural cell viability, microglial morphology, and proinflammatory signaling in response to controlled mechanical stress. A tri-culture system of neurons, astrocytes, and microglia is derived from P0/P1 Sprague Dawley rats and seeded onto a customized dogbone-shaped polydimethylsiloxane (PDMS) substrate. This geometric configuration and substrate composition enable the use of TBI-relevant strain rates without disrupting the gripping points, and allow the gauge area hosting the cells to experience a uniform strain field. The dogbone is adhered between two grippers that are contacted by a custom-built tension device to apply programmed uniaxial stress. Strain rates between 1 s<sup>-1</sup> to 30 s<sup>-1</sup> are evaluated at strains levels of 10% to 30%. Live-cell fluorescence imaging is performed before, during, and after strain application and is analyzed in conjunction with images of fixed samples stained for  $\beta$ -III Tubulin, GFAP, and Iba-1 to examine changes in neural cell health and microglial morphology. Additionally, relevant pro- and anti-inflammatory cytokines are quantified 24 hours after impact. This approach enables us to investigate the effects of precise, reproducible, and TBI-relevant mechanical strain on microglia. Our findings provide valuable insights into the mechanosensitive response of microglia and further our understanding of neuroinflammatory processes following a TBI.

**Disclosures:** E. Blick: None. C. Franck: None. A. Hai: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR216.10/G8

**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH R25NS124530  
ONR N000142112044

**Title:** Microglia in cortical spheroids exhibit sex-specific and injury severity-dependent differences following traumatic brain injury

**Authors:** \*R. D. GONZALEZ-CRUZ<sup>1,2,3</sup>, A. DEL TORO<sup>1</sup>, H. KESARI<sup>2</sup>, D. HOFFMAN-KIM<sup>1,2,3,4</sup>,

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**Abstract:** Traumatic brain injury (TBI) is a global health concern, contributing significantly to both mortality and long-term disability. In response to mechanical injury, microglia adopt reactive morphologies, migrate toward damaged areas, and secrete a mix of pro- and anti-inflammatory cytokines aimed at restoring homeostasis. However, when this inflammatory response persists, as often seen in moderate to severe TBI, it can lead to neurodegenerative

changes. Despite their clinical importance, the temporal dynamics of microglial activation and how they relate to injury severity are not completely understood. Here we employed a 3D rat cortical spheroid model, made from either male or female cortical cells, to investigate microglial responses to compressive mechanical injury induced by centrifugation as a function of sex, injury severity, and time post-injury. Spheroids were generated through the self-assembly of dissociated cortical cells derived from either female or male neonatal rats. Each spheroid was formed from 8000 cells and maintained in culture for 14 days. To simulate mechanical injury, a subset of spheroids underwent a single centrifugation event at angular velocities of 0, 209, or 419 rad/s for two minutes. Finite element modeling indicated that spheroids exposed to 209 and 419 rad/s experienced compressive strains of 18% and 35%, respectively. Changes in microglia activation and phagocytic phenotype were assessed via confocal imaging of Iba1 and CD68 immunostaining in a subset of fixed spheroids at 1, 3, 5, and 7 days post-injury. Cytokine secretion in injured spheroids was assessed by Mesoscale Discovery measurement of cytokines IL-6 and IL-10 and chemokine CXCL1. Statistical analysis used a 3-way ANOVA with a Tukey post hoc test. Microglia in spheroids subjected to 18% and 35% strain showed a significant increase in %CD68+ cells at 3 days post-injury, followed by significant decreases at 5 and 7 days in both sexes ( $p < 0.05$ ). In female spheroids, IL-6 and CXCL1 levels significantly increased by Day 3 and remained elevated at 18% but not 35% strains ( $p < 0.05$ ). Cytokines from male spheroids also peaked at Day 3 but at significantly lower levels than in females. These results highlight sex- and injury severity-dependent differences in microglial activation and phagocytic behavior, suggesting that microglial impairment may contribute to prolonged neuroinflammation and neurodegeneration following TBI.

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## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR216.11/G9

**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH NS118037

**Title:** Neuronal Dysfunction and Cognitive Deficits after Diffuse Brain Injury in mice are associated with Increased Phosphatase and Tensin Homolog Activation in Cortical Neurons

**Authors:** J. PACKER<sup>1</sup>, L. WANGLER<sup>2</sup>, A. DAVIS<sup>2</sup>, \*J. P. GODBOUT<sup>3</sup>;

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**Abstract:** Cognitive impairment can develop and even worsen in the years after traumatic brain injury (TBI), negatively affecting the quality of life and lifespan. Myriad studies show that TBI

reduces neuronal homeostasis and plasticity. For instance, we reported that diffuse TBI in mice suppressed pathways in cortical neurons associated neuronal homeostasis and plasticity 7 dpi. Moreover, microglial elimination (PLX5622) and stimulator of interferon genes (STING) ablation in microglia (mSTING<sup>-/-</sup>) both prevented the imbalance in neuronal homeostasis (single nuclei RNA-seq) and cognitive impairment induced by TBI. Thus, we sought to determine the pathways in cortical neurons shared by these two interventions and explore new targets to improve neuronal homeostasis after TBI. Here, we provide data from the integration of two snRNA-seq data sets from cortical neurons showing phosphatase and tensin homolog (PTEN) was enhanced by TBI and prevented by microglial/STING interventions. Specific genes associated with (PTEN)-regulated pathways were increased (*Pten*, *Gsk3b*, *Rock1*, *Rock2*) in neurons in the cortex after TBI while genes associated with the PI3k/AKT growth and survival pathway (*Akt3*, *Igf1r*, *Mapk1*) were suppressed. Next, PTEN was targeted for inhibition following TBI using Bisperoxovanadium-hoPIC (BPV). At 7 dpi, PTEN protein was increased in cortical neurons and this increase was attenuated by BPV intervention. TBI increased cortical inflammation and the reactivity of cortical astrocytes and microglia 7 dpi, but only increases in rod-shaped microglia were reduced by PTEN inhibition. Last, TBI-associated neuronal injury in the cortex and cognitive deficits in the NOL/NOR 7 dpi were reversed by the PTEN inhibition. Taken together, reducing PTEN signaling after TBI was effective in reducing neuronal dysfunction and cognitive impairment.

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## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR216.12/G10

**Topic:** D.04. Brain Injury and Trauma

**Support:** R01AG082207

**Title:** Knockdown of Acid-Sensing Ion Channel 1a in Neurons Attenuates Neuronal Damage Following Traumatic Brain Injury

**Authors:** \*Z. HUANG<sup>1</sup>, Y. ZHANG<sup>2</sup>, P. ZOU<sup>3</sup>, J. ZHANG<sup>4</sup>, X. ZONG<sup>5</sup>, Q.-G. ZHANG<sup>6</sup>;

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**Abstract: Background:** Traumatic brain injury (TBI) is a prevalent neurological condition affecting millions of people annually. Despite advances in acute management, there are currently no effective strategies to mitigate secondary neuronal damage following TBI. ASIC1a is a

proton-gated calcium channel that is activated in response to extracellular acidosis. Growing evidence suggests that prolonged activation of ASIC1a contributes to cell damage through calcium-mediated excitotoxicity. Since TBI is characterized by brain acidosis, and ASIC1a is primarily expressed in neurons, the present study aims to investigate the role of neuronal ASIC1a in TBI. **Methods:** C57BL/6J mice received AAV.CAP-B10-hSyn-5'miR-30a-shRNA2 (ASIC1a) or control AAV at 8 weeks of age via retro-orbital injection. A moderate TBI was induced via controlled cortical impact (CCI) 4 weeks after AAV administration to ensure peak AAV expression, and the brain tissues were harvested 1 week after CCI for histological analysis. **Results:** AAV.CAP-B10-hSyn-5'miR-30a-shRNA2 (ASIC1a) significantly reduced ASIC1a protein expression in the mouse cortex. Mice with neuronal ASIC1a knockdown exhibited reduced lesion volume following CCI, accompanied by attenuated neuronal loss, axonal damage, and demyelination in the perilesional cortical area. **Conclusions:** Our findings indicate that neuronal ASIC1a contributes to secondary damage after TBI. Thus, targeting neuronal ASIC1a may offer a novel therapeutic strategy to improve neurological outcomes following TBI.

**Disclosures:** Z. Huang: None. Y. Zhang: None. P. Zou: None. J. zhang: None. X. zong: None. Q. Zhang: None.

## Poster

### PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms

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**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH Grant 1R35NS116852-01  
NIH Grant 5R37NS077908-08

**Title:** Mechanisms of fluorescent protein quenching in programmed versus acute neuronal death

**Authors:** \*T. BALENA<sup>1</sup>, K. J. STALEY<sup>2</sup>;

<sup>1</sup>Massachusetts Gen. Hosp., Charlestown, MA; <sup>2</sup>Neurol., Massachusetts Gen. Hosp., Boston, MA

**Abstract:** We recently demonstrated that fluorescent protein (FP) quenching is a powerful early biomarker of apoptosis. This quenching is concurrent with prolonged increases in cytoplasmic membrane permeability (and thus increased admittance of membrane permeable dyes) and transient increases in caspase activity, as well as changes in cell morphology. However, the precise mechanism underlying this FP quenching remained unknown. Understanding this mechanism would shed further light on the processes occurring within cells during apoptosis, and allow for FP quenching to be better utilized as a biomarker of apoptosis.

We evaluated cell swelling and death in a chronically epileptic *in vitro* preparation using multiphoton microscopy. Organotypic hippocampal slice cultures were made from wild-type C57BL/6J mice on P6 and incubated *in vitro*. Slices were imaged with transgenic fluorophores such as TurboRFP, GFAP-GFP, and mStayGold to visualize healthy neurons and astrocytes, and

bath-applied fluorophores such as FLICA, NucView, and dihydroethidium (DHE) to assess apoptotic neurons.

Exposing slices to a sodium-free (high potassium, or High K) solution resulted in significant swelling of the neurons and, in turn, the entire slice. High K perfusion also caused widespread FP quenching, but washout of the High K solution with a standard solution restored FP-positivity in some (but not all) neurons. Astrocytes also swelled and quenched under High K conditions, and washout appeared to restore more FP-positivity than in neurons. Photobleaching of the FPs (from repeated laser light exposure) was found to be independent of FP quenching, as even highly photobleaching-resistant FPs quenched in High K. Elevated caspase activity was only observed after a long delay, indicating that it is not required for FP quenching. Application of the reducing agent N-acetylcysteine had no effect on quenching, suggesting that oxidative stress is not required, but early results with the oxidative stress sensor DHE suggest that oxidation may still be involved.

Overall, FP quenching is a useful early biomarker for both programmed and acute neuronal death, but the precise mechanisms underlying the quenching require further study. In the future, we intend to test redox-sensitive FPs (such as roGFP2), as well as FPs that are designed to generative reactive oxygen species. We also intend to test both programmed and acute models in *in vivo* mice.

**Disclosures:** T. Balena: None. K.J. Staley: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

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**Topic:** D.04. Brain Injury and Trauma

**Support:** KSHIRT 22-1A  
KSHIRT 24-2

**Title:** Understanding Toll Like Receptor Signaling induced neuronal death using metabolic modulators, MAP kinase and cell death cascade inhibitors

**Authors:** \*M. PANDEY<sup>1</sup>, L. WU<sup>2</sup>, C. MONCMAN<sup>1</sup>, D. A. ANDRES<sup>3</sup>;

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**Abstract:** Toll like receptor (TLR) signaling is important for sensing foreign antigens on the extracellular surface of mammalian cells. These receptors are also important for sensing endogenous molecules released from damaged or stressed cells known as damage associated molecular patterns (DAMPs). While TLR signaling has been extensively studied in immune cells, TLRs are also expressed in neurons and play crucial roles in neuronal function and brain

health. The understanding of TLR signaling in neurons is of immense importance contributing to neuroinflammation, pain and itch perception, and development of various neurodegenerative diseases. Here we explored the mechanism(s) responsible for TLR7/TLR9-mediated neuronal death. TLR7/9 stimulation lead to acute activation of JNK MAPK signaling in primary cortical neurons, leading to neuronal death after 48 hours. Inhibition of the JNK cascade by shRNA-mediated silencing of MKK4 and MKK7 expression (essential upstream regulators of JNK) or pharmacological blockade provided significant protection against TLR7/9-induced neuronal death. Activation of JNK MAPK pathway occurs within minutes of TLR stimulation, but days before neuronal death, leading us to explore the connection between these processes. As a decrease in ATP levels in injured neurons has been found to proceed axon degeneration, and calpain activation is responsible for breakdown of axonal structures, we examined the role of energy deficit and calpain activation in TLR-degeneration. Methyl-pyruvate treatment, which supports ATP levels in injured neurons, provided significant protection against TLR7/9-mediated neuronal loss. Surprisingly, many cell death cascade inhibitors including calpain and caspase did not protect against TLR7/9 induced neuronal death. Taken together, these data suggest that TLR7/9 activates a complex signaling pathway involving both MAPK signaling and metabolic compromise to induce neuronal death and highlight the need for improved understanding of how innate immune responses in the CNS drive neuronal damage.

**Disclosures:** M. Pandey: None. L. Wu: None. C. Moncman: None. D.A. Andres: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

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**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH R56 NS129438  
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Falk Medical Research Trust

**Title:** Neuroprotective role of proliferative reactive astrocytes in synaptic remodeling after traumatic brain injury

**Authors:** \*L. K. PRADHAN, A. E. GOWAN, F. YUAN, X. GAO;  
Neurolog. Surgery, Indiana Univ. Sch. of Med., Indianapolis, IN

**Abstract:** Astrogliosis, marked by gene expression changes, hypertrophy, and proliferation, is a hallmark response to traumatic brain injury (TBI). The functional significance of proliferative reactive astrocytes as neuroprotective or neurotoxic remains debated, with mechanisms unclear. Our current study aims to elucidate the mechanism underlying reactive astrocyte proliferation and its neuroprotective impact on hippocampal function post-TBI. Previously, our findings



revealed a selective upregulation of platelet-derived growth factor receptor alpha (PDGFR $\alpha$ ) in proliferating astrocytes after TBI. Using triple immunostaining for PDGFR $\alpha$ , GFAP, and Ki67, we quantified astrocyte proliferation and found that  $90.27\% \pm 3.83\%$  of proliferating astrocytes expressed PDGFR $\alpha$  (male mice, n=5). While PDGFR $\alpha$  is known to regulate CNS vascular integrity, myelination, neurogenesis, and tumorigenesis, its involvement in TBI-induced astrogliosis remains unclear. We hypothesize that PDGFR $\alpha$  signaling regulates reactive astrocyte proliferation and contributes to neuroprotection by preserving synapses and promoting synaptogenesis. To this end, we generated conditional PDGFR $\alpha$  knockout (PDGFR $\alpha$ -cKO) mice and induced moderate TBI via controlled cortical impact. Astrocyte proliferation and synaptic changes were assessed by immunostaining, while functional recovery was evaluated using the elevated plus maze to measure anxiety-like behavior. Results of our study show that PDGFR $\alpha$  cKO mice significantly reduced reactive astrocyte proliferation, as indicated by BrdU and GFAP co-labeling (male mice, n=5). Synaptic density, measured by synaptophysin-positive puncta in the dentate gyrus, was significantly reduced in the ipsilateral hippocampus of TBI PDGFR $\alpha$ -cKO mice compared to sham controls (male mice, n=5). Furthermore, PDGFR $\alpha$ -cKO mice displayed increased impulsivity in the EPM, spending more time and traveling greater distances in the open arms post-injury (male mice, n=5). In a nutshell, our findings underscore the essential role of PDGFR $\alpha$  signaling in driving reactive astrocyte proliferation and promoting synaptic preservation and functional recovery after TBI. Future direction of our study includes the use of inducible conditional knockout mice to minimize potential confounding effects of PDGFR $\alpha$  deletion in GFAP-expressing cells post-TBI, enabling identification of critical windows during which its signaling supports synaptic integrity and functional recovery.

**Disclosures:** L.K. Pradhan: None. A.E. Gowan: None. F. Yuan: None. X. gao: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.16/G14

**Topic:** D.04. Brain Injury and Trauma

**Support:** R01NS097750  
R37NS069861

**Title:** Tlr4 inhibition restores excitation-inhibition balance and preserves neurogenesis following traumatic brain injury

**Authors:** \*R. JABERI<sup>1</sup>, V. SANTHAKUMAR<sup>2</sup>;

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## **Abstract: Abstract**

Mammalian dentate neurogenesis continues into adulthood and is regulated by environmental

cues, learning, and neurological insults like traumatic brain injury (TBI). Previously, we identified that TBI enhances Toll-like receptor 4 (TLR4) signaling, which increases network excitability and cognitive deficits. Blocking TLR4 reduced improved posttraumatic outcomes. Since TLR4 is expressed in the dentate neurogenic niche, here we examined whether TLR4 regulation of injury-induced neurogenesis, could contribute to posttraumatic neuropathology. Immunohistochemistry in wild-type FPI and sham mice following EdU treatment to assess cell proliferation identified a post-FPI increased in dentate cell proliferation, which was reduced by in vivo treatment with TLR4 inhibitor CLI-095 (0.5 mg/kg i.p.) early after FPI. Co-labeling revealed that EdU+ cells in the CLI-treated group were predominantly Nestin+ progenitors, with fewer cells co-expressing DCX or GFAP, suggesting altered lineage dynamics. Adult Nestin-CreERT2:tdTomato mice underwent moderate fluid percussion injury (FPI, 2 atm) or sham surgery followed by tamoxifen (75 mg/kg, 3 consecutive days after FPI) induction, and were treated with the CLI-095 or vehicle and evaluated for altered neurogenesis and circuit integration of adult-born granule cells (abGCs). In whole-cell patch clamp recordings from labeled abGCs and unlabeled mature granule cells one month after FPI, abGCs in mice after FPI received larger amplitude perforant path evoked excitatory post-synaptic currents (EPSCs) and had elevated excitation/inhibition (E/I) ratios. CLI-095 treatment normalized the E/I ratio by increasing inhibitory post-synaptic current (IPSC) amplitude, resulting in values comparable to sham controls. Analysis of intrinsic membrane property identified accelerated physiological maturation of abGCs after FPI which was limited by CLI-095 treatment. Together, our data suggest that TLR4 signaling enhances injury-induced proliferation and accelerates functional maturation of abGCs with aberrant excitability. Inhibiting TLR4 signaling with CLI-095 mitigates these effects, normalizes circuit integration, and preserves developmental trajectories of adult-born neurons. These findings support a multifaceted role for TLR4 in regulating posttraumatic neurogenesis and identify it as a potential therapeutic target. **Keywords:** Fluid Percussion Injury, Neurogenesis, Toll-like Receptor 4 (TLR4), Adult-born Granule Cells, CLI-095

**Disclosures:** R. Jaber: None. V. Santhakumar: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.17/G15

**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH: NINDS R01 NS076715  
DoD: W81XWH-16-0175  
Massey Foundation

**Title:** Molecular regulators of mitochondrial dynamics are disrupted in primary neurons following axonal stretch injury

**Authors: \*R. L. SPEAS;**

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**Abstract:** Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Following head trauma, the secondary injury mechanisms, including energy deficit, excitotoxicity, and ionic imbalance, contribute to neuronal death that occurs for minutes to years. Mitochondria play a central role in maintaining cellular homeostasis and meeting energetic requirements of neurons through tight regulation of coordinated cycles of fission, mediated by Drp1, and fusion, mediated by Opa1, known collectively as mitochondrial dynamics. We hypothesize that the disruption of these key molecular regulators of mitochondrial dynamics plays a causal role in neuronal death following TBI. To test this, we used an in vitro model of axonal stretch injury (ASI), which replicates the mechanical impact of head trauma. Primary mouse cortical neurons are grown on a silicon membrane, which is subjected to uniaxial strain that stretches the neuronal cell bodies and processes. Using mild, moderate, and severe injuries, we evaluated mitochondrial morphological disruption within neurons using confocal microscopy and our validated machine learning classifier up to 24 hours post-ASI. We evaluated cell viability using a lactate dehydrogenase assay (LDH) and measured mitochondrial dynamic regulators and related proteins at corresponding timepoints. Our preliminary results show a shift toward punctate and swollen mitochondrial morphology at all injury severities ( $n = 3-4$ ,  $p < 0.05$ ). This shift coincides with upregulated Drp1 and increased proteolytic cleavage of Opa1 via Oma1 at 2- and 4-hours post-ASI in moderate and severe injury ( $n = 3-4$ ,  $p < 0.01$ ), indicating a differential disruption in molecular regulators of mitochondrial dynamics. LDH-indicated cell death increases with injury severity ( $n = 3$ ,  $p < 0.05$ ). Ongoing studies are investigating the mechanistic role of Drp1 and Oma1 in mitochondrial morphologic disruption and cell viability after ASI using genetic knockouts at critical timepoints.

**Disclosures: R.L. Speas:** None.

**Poster**

**PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.18/G16

**Topic:** D.04. Brain Injury and Trauma

**Support:** R37HD059288

**Title:** Microglia Depletion Improves Hippocampal Circuit Function After Mild Traumatic Brain Injury in Male Mice

**Authors: \*S. A. S. DELCY<sup>1</sup>, A. FARRUGIA<sup>2</sup>, A. S. COHEN<sup>3</sup>;**

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**Abstract:** Traumatic brain injury (TBI) affects over 69 million people every year, and mild traumatic brain injury (mTBI) accounts for 70-90% of cases. TBI involves two phases: the initial mechanical damage to brain tissue from the impact followed by secondary injury cascades such as neuroinflammation, which contribute to the development of long-term deficits. Neuroinflammation is triggered mainly by the activation of microglia and has been linked to recovery in the short term and neurodegeneration in the long term. Microglia mediate neuroinflammation through the release of cytokines such as TNF- $\alpha$ , which can impact synaptic function and neuronal activity. Our study investigates the role of microglia depletion in restoring neuronal function after mTBI in male mice, with a focus on identifying specific pro-inflammatory modulators that contribute to the injury-induced Excitation/Inhibition imbalance in the hippocampal circuitry. We demonstrate that microglia depletion using PLX3397 for 7-10 days after mTBI significantly reduces microglia and restores network excitability in area CA1 and the dentate gyrus (DG), thus mitigating cognitive dysfunctions. We also highlight subregion-specific differences in DG. We show that using the immunomodulator, thalidomide, in slices from injured animals restores excitability, similarly to microglia depletion, by targeting pre-synaptic dysregulation in the hippocampal circuitry. Our findings further suggest that microglia depletion, and more specifically cytokine modulation offer promising therapeutic avenues for improving long term deficits post-TBI by targeting synaptic dysfunction. These new insights contribute to our understanding of the altered microglial-neuronal relationship in TBI and highlight potential targets for future interventions that can specifically address detrimental effects of chronic inflammation after injury.

**Disclosures:** S.A.S. Delcy: None. A. Farrugia: None. A.S. Cohen: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.19/H1

**Topic:** D.04. Brain Injury and Trauma

**Title:** Traumatic brain injury impairs cardiovascular function independent of cerebral hypoperfusion

**Authors:** C. T. GUMBO<sup>1</sup>, D. CORBIN<sup>2</sup>, N. ZHANG<sup>3</sup>, S. L. MCLAUGHLIN<sup>4</sup>, S. MUTHU<sup>3</sup>, V. SUNDARARAJAN<sup>3</sup>, K. KARELINA<sup>1</sup>, \*Z. M. WEIL<sup>5</sup>;

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**Abstract:** Traumatic brain injury (TBI) is a prevalent neurological condition with long-term consequences that extend beyond the brain. Individuals with a history of TBI are at increased risk for cardiovascular complications, but the mechanisms remain unclear. Here, we tested whether chronic cerebral hypoperfusion, modelled via bilateral carotid artery stenosis (BCAS),

exacerbates cardiac dysfunction following TBI. Male and female Swiss Webster mice (8-10 weeks old) were assigned to sham, BCAS, TBI, or BCAS+TBI groups. Cerebral blood flow (CBF) was measured using laser speckle contrast imaging at baseline and following acetazolamide challenge to assess cerebrovascular reserve. Neuroinflammation was evaluated in the insular cortex, a key autonomic hub, via IBA-1 and GFAP immunostaining. Cardiac function was assessed using transthoracic echocardiography, and myocardial morphology was examined by hematoxylin and eosin staining. TBI significantly impaired cardiac function in both sexes, whereas BCAS alone did not. Both TBI and BCAS+TBI mice showed structural alterations in cardiomyocytes, including reduced nuclear density and increased nuclear size. BCAS alone induced robust gliosis in the insular cortex without cardiac impairment, suggesting a subclinical neuroinflammatory priming effect. Combined BCAS and TBI further reduced CBF and cerebrovascular reactivity, with amplified glial activation in the insula. These findings suggest that TBI-induced cardiac dysfunction is associated with neuroinflammation in central autonomic circuits, and that preexisting cerebral hypoperfusion may enhance susceptibility. This work underscores the brain-heart axis as a critical pathway in post-TBI morbidity, and highlights cerebrovascular health as a potential modifier of cardiac outcomes after brain injury.

**Disclosures:** K. Karelina: None. Z.M. Weil: None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.20/H2

**Topic:** D.04. Brain Injury and Trauma

**Title:** Elucidating the mechanistic link between acrolein pathology and dysregulation of glutamate uptake transporter-1 (GLT-1) following blast-induced traumatic brain injury

**Authors:** \*R. STINGEL<sup>1</sup>, J. PAGE<sup>3</sup>, R. SHI<sup>2</sup>;

<sup>1</sup>Purdue Univ., West Lafayette, IN; <sup>2</sup>Purdue Univ., West Lafayette, IN; <sup>3</sup>Harvard Univ., Boston, MA.

**Abstract:** Mild blast-induced traumatic brain injury (bTBI) often goes undiagnosed due to the absence of acute neurological symptoms. Although individuals who experience these injuries typically do not seek treatment, they tend to present similar cognitive, psychological, and behavioral manifestations to those with “more severe” TBIs at later time points. These observations necessitate a better understanding of the mechanisms underlying bTBI as doing so will not only further our understanding of neurotraumatic injury, but could also be used to improve diagnostic capabilities and develop viable treatments. Neuronal injury from traumatic events, such as TBI and spinal cord injury, produce immediate neuronal damage (primary injury), which is followed by a series of secondary biochemical cascades (secondary injury) that can last for minutes to years thereafter, thereby worsening injury outcomes. Two notable pathologies within the early stages of secondary injury are excitotoxicity and the formation of

reactive aldehyde species (RAS) from oxidative stress-induced lipid peroxidation. RAS such as acrolein can promote neuronal damage by binding to and inducing conformational changes in proteins - leading to dysfunction. The purpose of this study was to determine if acrolein underlies excitotoxicity following bTBI by interacting with glutamate transporter-1 (GLT-1), the primary regulator of extracellular glutamate levels. Using an in vivo rat model of bTBI, we show that 1) decreased GLT-1 levels correlated with increased acrolein levels, 2) application of exogenous acrolein in the absence of bTBI also led to decreased GLT-1 levels, 3) acrolein interacts with GLT-1 following bTBI, and 4) administration of acrolein scavenger phenelzine protected GLT-1 levels. These findings suggest that acrolein is capable of damaging GLT-1 after bTBI and independent of injury.

**Disclosures: R. Stingel:** None.

## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.21/H3

**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH Grant R01NS109075  
NIH grant R01AG079303

**Title:** Selective targeting of activated cytosolic cathepsin B by the Z-Arg-Lys-AOMK inhibitor in traumatic brain injury mice and improvement of behavioral motor dysfunction

**Authors:** \*V. Y. HOOK<sup>1</sup>, S. PODVIN<sup>6</sup>, J. B. FLORIO<sup>7</sup>, B. J. SPENCER<sup>7</sup>, E. GUZMAN<sup>2</sup>, C. MOSIER<sup>9</sup>, V. PHAN<sup>2</sup>, M. C. YOON<sup>3</sup>, J. ALMALITI<sup>4</sup>, W. GERWICK<sup>5</sup>, A. O'DONOGHUE<sup>2</sup>, R. RISSMAN<sup>8</sup>;

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**Abstract:** Traumatic brain injury (TBI) is an important risk factor that facilitates Alzheimer's disease (AD) and neurodegeneration. Behavioral deficits and brain neuropathology has been shown to involve the lysosomal protease cathepsin B, which undergoes translocation to the cytosol due to lysosomal leakage, as shown in TBI and AD models. Deletion of the cathepsin B gene or chemical inhibition of cathepsin B have been shown to ameliorate TBI-induced motor dysfunction and brain tissue loss in mice, and improves memory deficit in an Alzheimer's mouse model. But the distinction of the role of cytosolic cathepsin B in these brain disorders, compared to the normal lysosomal cathepsin B, has not yet been fully assessed. Therefore, this project developed and evaluated a selective neutral pH inhibitor of cytosolic cathepsin B based on its

unique cleavage properties at neutral pH 7.2 of the cytosol compared to the acidic pH 4.6 of the lysosome. The novel Z-Arg-Lys-AOMK inhibitor potently inhibits neutral cathepsin B activity at nM levels, but not at acidic pH 4.6 conditions. *In vivo* evaluation of this inhibitor to target cytosolic cathepsin B resulting from lysosomal leakage during TBI was investigated in the controlled cortical impact (CCI) model in mice. CCI-TBI resulted in motor deficit demonstrated by the rotarod assay, brain tissue lesion, and disorganization of the hippocampus. Notably, CCI-TBI increased cytosolic cathepsin B activity in brain cortex in the ipsilateral brain hemisphere that received the CCI-TBI injury, with a concomitant decrease in the lysosomal fraction. While the normal lysosomal distribution of cathepsin B was observed by its discrete localization in brain cortical cells, CCI-TBI resulted in a more diffuse cellular distribution of cathepsin B consistent with its translocation to the cytosol. Administration of Z-Arg-Lys-AOMK to the CCI-TBI mice resulted in reduction of the increased cytosolic cathepsin B activity induced by CCI-TBI. Furthermore, the Z-Arg-Lys-AOMK inhibitor resulted in reduction of motor function deficit resulting from CCI-TBI. These findings demonstrate that elevated cytosolic cathepsin B activity participates in CCI-TBI brain injury. (This research was supported by NIH grant R01NS109075 awarded to VH and grant R01AG079303 awarded to RR.)

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## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.22/H4

**Topic:** D.04. Brain Injury and Trauma

**Title:** Analyzing morphological changes to microglia after blast injury in vitro

**Authors:** \*N. KRISHNAN<sup>1</sup>, J. MARTINEZ<sup>5</sup>, S. MUFTI<sup>2</sup>, M. CHEN<sup>1</sup>, C. ADAM<sup>1</sup>, T. B. BEAUCLAIR<sup>3</sup>, J. MILES<sup>1</sup>, R. SHI<sup>4</sup>;

<sup>2</sup>Biomed. Engin., <sup>1</sup>Purdue Univ., West Lafayette, IN; <sup>3</sup>Purdue Univ., Lafayette, IN; <sup>4</sup>Depat. Basic Med. Sci., Purdue Univ., West Lafayette, IN; <sup>5</sup>Ctr. for Paralysis Res., Ctr. for Paralysis Research, Purdue University, West Lafayette, IN 47907., Lafayette, IN

**Abstract:** Blast traumatic brain injury (bTBI), or damage to the brain caused by shock wave exposure, is highly prevalent amongst both military personnel and civilians. Mild blast injuries that often go undiagnosed can increase the likelihood of developing neurodegenerative diseases like Alzheimer's Disease (AD). Understanding the cellular mechanisms connecting injury to AD is critical to preventing post-bTBI neurodegeneration. One of the key shared pathologies between bTBI and AD is neuroinflammation, which includes activation of the immune cells of the brain called microglia that then switch from having a ramified morphology to an amoeboid one. Moreover, neuroinflammation has been shown to be connected to other mechanisms shared

between bTBI and AD, including elevation in levels of a toxic aldehyde called acrolein. Acrolein can alter protein expression in microglia and previous work from our lab has shown that it can also promote higher levels of tumor necrosis factor alpha (TNF- $\alpha$ ), a pro-inflammatory cytokine that can both be released by and activate microglia. To understand how post-injury neuroinflammation and toxic factors like acrolein work together to promote AD, it is critical to study microglial activation after blast injury. While microglial activation after bTBI has previously been studied *in vivo*, studying this phenomenon *in vitro* isolates microglia from factors like the peripheral immune system, allowing a cellular-level understanding of the microglial response to shock wave exposure that can help untangle the mechanisms observed *in vivo*. To this end, in this study primary murine embryonic cortical cultures were subjected to mild blast injuries using an established *in vitro* model of blast injury employing a shock tube. The cultures were then subject to immunofluorescent labeling 24 hours after injury. Microglial activation was analyzed by using both immunofluorescence and morphology to identify microglia and by then quantifying the area of microglia subject to blast injury and of procedure-matched control microglia. The average area of microglia subject to blast injury were higher than those of control microglia. This morphological change suggests a more activated phenotype 24 hours post-injury, and to our knowledge, this is the first investigation of microglial morphology after mild blast injury *in vitro*. This finding is consistent with previous work from our lab showing elevation of both TNF- $\alpha$  and acrolein 24 hours post-blast injury *in vitro*. Future work will look to characterize microglial phenotype after acrolein treatment to illuminate what aspects of microglial activation state after blast injury may be mediated by acrolein.

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## **Poster**

### **PSTR216: Traumatic Brain Injury: Cellular and Molecular Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR216.23/H5

**Topic:** D.04. Brain Injury and Trauma

**Support:** NIH Grant EY029313  
NIH Grant R01EY032908  
NIH Grant T32 EY013360

**Title:** Investigating retinogeniculate organization in the visual thalamus after monocular crush injury and the role of PTEN-KO in healthy neurons

**Authors:** \***S. MCCracken**<sup>1</sup>, J. L. MORGAN<sup>2</sup>, P. R. WILLIAMS<sup>3</sup>;  
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**Abstract:** Retinal ganglion cell (RGC) death, primarily in the form of glaucoma, is a major cause of visual impairment. Progress is being made in regenerative techniques that replace RGCs and encourage new axon growth. However, it is not known whether the primary target of RGCs, the dorsal lateral geniculate nucleus (dLGN), is able to form new functional connections with RGCs in adult mammals. We asked whether mouse RGCs from one eye might spread to innervate neighboring dLGN after RGCs from the other eye had been removed. Using a novel technique to assess the entire LGN in 3D, we performed monocular optic nerve crush (ONC) axon injury, which effectively severs RGC axons from only one eye, and gave time for the dLGN to respond. There was a clear decrease in volume of the dLGN contralateral to the injury that could be detected one month after denervation and continued to increase at three and six months after denervation (contralateral to ONC eye: 3-month post crush (mpc)= -30.8% +/- 8% reduction in volume, 6mpc= 41.0% +/- 7%). Surprisingly, the dLGN ipsilateral to the ONC injury also had a slight reduction volume (3mpc= -14.6% +/- 11%, 6mpc = -8.89% +/- %: N=5, 5). Our study argues that dLGN plasticity, to the extent that it might exist, does not extend to allowing RGC axons to cross the boundaries of eye-specific territories. Rather, we found that both dLGN's shrinks in size after monocular ONC. It is also not known whether efforts to restore vision by encouraging the regrowth of RGCs will result in functional synaptic connections being formed between the eye and the visual thalamus. Many studies have determined that knocking out or reducing expression of the PTEN gene, which is a tumor suppressor gene that regulates the mTOR pathway, is a method for increasing cellular plasticity. In RGC regeneration specifically, PTEN-KO has been used with overexpression of CNTF to lead to extensive axon regeneration of RGCs, which do not regenerate spontaneously. The application of this regeneration cocktail appeared to have a general destabilizing effect on RGC axons. More importantly, RGC cell bodies in the retina were extensively damaged and many were even dead. These results imply that PTEN-KO along with CNTF can be detrimental to healthy neurons. While these treatments are being applied and attempted to be used for human therapies, this study is important by shedding light on potential limitations of this treatment.

**Disclosures:** S. McCracken: None. J.L. Morgan: None. P.R. Williams: None.

## **Poster**

### **PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.01/H6

**Topic:** D.04. Brain Injury and Trauma

**Title:** Systematic review of cognitive-motor interactions in middle-aged adults post-concussion

**Authors:** A. BISHNOI<sup>1</sup>, \*M. E. HERNANDEZ<sup>2</sup>;

<sup>1</sup>Physical Therapy, Kean Univ., Union, NJ; <sup>2</sup>Biomed. and Translational Sci., UIUC, Urbana, IL

**Abstract: Background and Aim:** Dual-task walking is often used to evaluate cognitive impairment and fall risk. Understanding these dual task effects can provide insights into

cognitive-motor interactions in individuals with a history of concussion. This study aims to systematically review the literature to assess the effects of dual-task conditions on spatiotemporal gait parameters in adults with and without concussion. **Methods:** Keyword search was performed in 5 databases: PubMed, CINHAL Academic Ultimate, PsychInfo, Scopus, Web of Science (01/2000-11/2024). We performed search algorithm including all possible combinations of keywords. Full-text articles were examined further using forward/backward search. Studies were thoroughly screened using the following inclusion criteria: had a study design of cross-sectional, RCT, prospective, retrospective or pre-post; population: adults  $\geq 40$  years old with a brain injury, task: any type of dual task or concurrent task while walking, main outcome measures: spatial and temporal gait characteristics including stride length, stride time, step length, step width, step time, stance time, swing time, single support time, double support time, or cadence, peer-reviewed article, and publication language: English. Studies were excluded from the review if they contained one or more of the following exclusion criteria: studies published before 2000, population:  $< 40$  years old, experimental groups contained only healthy adults, studies that did not include any spatial or temporal gait characteristics. A standardized data extraction form was used to collect the following methodological outcome variables from each of the included studies: author, year, population, age, sample size, and spatiotemporal gait parameters such as gait speed, step length, double limb support, cadence, stride length. **Results:** Five studies were reviewed, encompassing a total of 180 post-concussed participants and 65 matched non-concussed controls who met the inclusion criteria. The single-task condition involved usual walking, while dual-task walking included six tasks performed concurrently: visual Stroop, Stroop with head turns, verbal fluency, serial subtraction by three, walking with a narrow base of support, and walking while holding a cup of water. Among these, serial subtraction, a working memory task, and Stroop with head turns demonstrated the most noticeable changes in gait speed among post-concussed participants compared to controls. **Conclusion:** The findings suggest that working memory tasks, such as serial subtraction while walking, may be sensitive tool for detecting dual-task gait changes in post-concussed individuals.

**Disclosures:** A. Bishnoi: None. M.E. Hernandez: None.

## **Poster**

### **PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.02/H7

**Topic:** I.10. Human Learning and Cognition

**Support:** NINDS (NIH) Grant R43NS132718-01  
NIH Grant 1S10-OD034302-01  
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VA Grant NEUC-044-06S

**Title:** Retraining dorsal visual pathways improves cognitive skills after a mild traumatic brain injury

**Authors:** \*T. LAWTON<sup>1</sup>, J. SHELLEY-TREMBLAY<sup>2</sup>, R. R. LEE<sup>3</sup>, M.-X. HUANG<sup>4</sup>;  
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**Abstract:** Currently, there are no proven solutions to remediate cognitive deficits in people with a mild traumatic brain injury (mTBI). One common issue is visual timing deficits, which may be due to processing deficits in dorsal visual pathways. **Methods:** This study investigates whether a new intervention (*PATH* + *DigitMemory* (*DM*)) aimed at improving these visual timing deficits is more effective than conventional cognitive therapies that either remediate: 1) pattern discrimination deficits (ventral visual pathway): Orientation Discrimination (OD) + *DigitMemory*, or 2) working memory deficits using *ReCollect* task, for 24 subjects between the ages of 23-60 years old. This study tests the ability of three different cognitive therapies to improve the primary outcome: visual working memory (VWM), and secondary outcomes: processing speed (PS), auditory working memory (AWM), and selective attention in mTBI subjects based on neuropsychological tests administered before and after 36 30-minute training sessions Monday, Wednesday and Friday mornings. **Results:** On average, the *PATH* group exhibited a 35% improvement in VWM, compared to 15% for *ReCollect* and 5% for OD. A repeated-measures ANOVA found that improving dorsal stream function improved VWM significantly more than found after the other two interventions. Moreover, the *PATH* group exhibited marked improvements in PS, AWM, and selective attention. The results reveal the importance of strengthening dorsal pathways more than conventional cognitive therapies to improve cognitive skills after mTBI. A biomarker, MagnetoEncephaloGraphy (MEG) functional imaging-based neurophysiological recordings, using an N-Back task, verified these improvements, as well as revealing two new cortical areas, hippocampus and anterior temporal lobe, improved in function, cortical areas not found previously after *PATH*, suggest that *PATH+DM* training extends its impact to memory consolidation and retrieval (patent pending). The other cortical areas in the vision (superior occipital gyri), attention (ACC and PCC), and executive control (dlPFC) networks had stronger POST- vs. PRE-intervention MEG responses, found previously after *PATH*, underscores *PATH*'s effect on executive function and attentional control. These areas play a central role in working memory and cognitive flexibility, suggesting that *PATH+DM* training strengthens core neural substrates responsible for task coordination and response inhibition. **Conclusions:** The data from this controlled validation study are very promising for a new method improving the brain's timing, more effective than conventional therapies, to improve cognitive deficits in mTBI patients.

**Disclosures:** T. Lawton: A. Employment/Salary (full or part-time): Perception Dynamics Institute. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Perception Dynamics Institute. J. Shelley-Tremblay: None. R.R. Lee: None. M. Huang: None.

**Poster**

**PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.03/H8

**Topic:** D.04. Brain Injury and Trauma

**Title:** Neural patterns of self-efficacy and resulting changes after cognitive rehabilitation in mild traumatic brain injury

**Authors:** \*E. N. TRIBBEY<sup>1</sup>, C. L. PHILIPPI<sup>2</sup>;

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**Abstract:** Mild traumatic brain injury (mTBI) often leads to cognitive impairments which can significantly affect recovery outcomes. Evidence-based research has indicated that cognitive rehabilitation programs can lead to significant improvement in psychological symptoms as well as psychosocial and vocational functioning in mTBI. Clinical research further suggests that self-efficacy, or the belief in one's capacity to achieve goals, may play a critical role in further improving cognitive rehabilitation outcomes. However, to our knowledge, no studies have investigated the neural underpinnings of self-efficacy following cognitive rehabilitation in mTBI. We used resting-state fMRI data for 37 individuals with mTBI before and after cognitive rehabilitation. We computed resting-state functional connectivity (rsFC) for self-related brain regions of interest associated with self-efficacy including the medial prefrontal cortex, anterior cingulate cortex, precuneus, and ventral striatum. Analyses investigated the relationship between self-efficacy and rsFC before and after cognitive rehabilitation in mTBI and examined whether rsFC mediated the relationship between self-efficacy at baseline and treatment response (i.e. psychological distress symptoms) following cognitive rehabilitation in mTBI. All rsFC findings were corrected for multiple comparisons at the whole brain level (pFWE < .05). There was significant relationship between self-efficacy and rsFC between the anterior cingulate cortex and right anterior medial prefrontal cortex at baseline. Cognitive rehabilitation was associated with increased rsFC between the medial prefrontal cortex and right supramarginal gyrus, and between the precuneus and right premotor cortex, right dorsal precuneus, and right inferior parietal lobule. Although greater self-efficacy was associated with fewer symptoms of psychological distress after rehabilitation, rsFC results did not mediate the relationship between these variables. Our findings of increased connectivity in motor, attention, and default mode networks after rehabilitation may reflect improvements in cognitive or behavioral functioning in individuals with mTBI. Future research should incorporate self-efficacy-enhancing strategies into rehabilitation programs to further support recovery and optimize outcomes.

**Disclosures:** E.N. Tribbey: None. C.L. Philippi: None.

**Poster**

**PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.04/H9

**Topic:** I.05. Working Memory

**Title:** How Concussion Status, Sex, and Age Influence Perceptual-Cognitive Function: A NeuroTracker Analysis

**Authors:** \*E. L. SKAUG<sup>1</sup>, T. SNOWDEN<sup>2</sup>, B. R. CHRISTIE<sup>3</sup>;

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**Abstract: Background:** Diagnosing and managing concussion is challenging for practitioners because of variability in concussion symptoms between individuals and the subjective nature of current assessment tools. NeuroTracker (NT) is a 3-dimensional multiple-object tracking test that objectively quantifies perceptual-cognitive processing and may serve as a useful tool for objective assessment of concussion. **Objectives:** This study aimed to create a set of normative NT scores based on age, sex, and concussion status (concussion and non-concussed) and to investigate whether sex, age, and concussion-related variables can predict NT performance. **Methods:** We retrospectively analyzed data from 1,251 individuals collected between 2009 and 2021 at University of Victoria Concussion Lab. NT scores were categorized according to age, sex, and concussion status. Normative measures of NT scores were created by calculating Z-scores and analyzed by plotting standard normal curves. Independent mean difference and Hedges'  $g$  were used to assess effect sizes of concussion status on NT scores. Two-tailed  $t$  tests were used to assess the significance of concussion status on NT scores. Linear and multiple regressions and linear correlation were used to assess the relationship between NT scores and concussion-related variables. A decision tree using concussion status, age, and sex was used to predict NT performance. **Results:** Medium to large effect sizes were observed between concussed and non-concussed participants in the following groups: males aged 13 to 24 years and 55 to 64 years and females aged 19 to 24 years and 45 to 54 years. Furthermore, NT scores increase from ages 5 to 18 years, peak between 19 and 34 years, and then decrease with age across both sexes. NT scores most strongly correlated with King-Devick scores ( $r = -0.28$ ), symptom severity ( $r = -0.24$ ), and standardized concussion assessment score ( $r = 0.37$ ). A multiple regression model explains approximately 22.42% of the variation in NT. The decision tree classified NT performance with 70.1% accuracy. **Conclusions:** NeuroTracker is sensitive to concussion-related impairments in perceptual-cognitive processing across the lifespan. Normative NT scores stratified by age, sex, and concussion status may support objective concussion assessment and monitoring.

**Disclosures:** E.L. Skaug: None. T. Snowden: None. B.R. Christie: None.

**Poster**

**PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.05/H10

**Topic:** D.04. Brain Injury and Trauma

**Support:** Mitacs Accelerate  
Canadian Institutes of Health Research  
Eldercare Foundation

**Title:** Train your brain: Evaluating the impact of three-dimensional multiple object tracking on cognitive function and quality of life in traumatic brain injury survivors

**Authors:** \*I. TUCCI<sup>1</sup>, J. MORRISON<sup>2</sup>, T. SNOWDEN<sup>3</sup>, E. SKAUG<sup>2</sup>, I. ENCINA<sup>2</sup>, K. STERNIG<sup>2</sup>, B. R. CHRISTIE<sup>1</sup>;

<sup>1</sup>Div. of Med. Sci., <sup>2</sup>Univ. of Victoria, Victoria, BC, Canada; <sup>3</sup>Med. Sci., Univ. of Victoria, Sidney, BC, Canada

**Abstract:** Background: Traumatic brain injury (TBI) remains a leading global cause of long-term disability worldwide, affecting approximately 69 million individuals annually. Despite this prevalence, accessible and effective recovery interventions are limited. Three-dimensional multiple object tracking (3D-MOT) is a visual-spatial cognitive training tool designed to engage working memory, distributed attention, and complex motion integration. This study explores the potential of 3D-MOT to improve cognitive function and quality of life in TBI survivors.

Methods: In collaboration with the Victoria Brain Injury Society, 20 adults with a history of moderate to severe TBI—each at least one year post-injury—were recruited for this study. Participants were randomized into the 3D-MOT intervention or waitlist control group. Pre- and post-intervention assessments involved neuropsychological testing and standardized self-report questionnaires, including the Mayo Portland Adaptability Inventory 4 and Sport Concussion Assessment Tool 5. The intervention group completed 3D-MOT training at home twice per week over five weeks. Data was analyzed using estimation statistics with 5,000 bootstrap samples applying bias-corrected and accelerated confidence intervals. Results are reported as mean differences (pre-post intervention mean difference [95% CI]) and (pre-post control period mean difference [95% CI]). Findings: Twenty participants (13 male, 7 female) completed the study. The 3D-MOT group demonstrated a 27.1% reduction in daily life challenges (-20.10 [95% CI: -36.22, -3.77]); (-5.40 [95% CI: -24.50, 17.31]) and a 25.1% decrease in symptom severity (-26.40 [95% CI: -48.73, 1.75]); (-4.00 [95% CI: -30.10, 23.46]). Intervention participants also improved 10.0% in verbal fluency (6.9 [95% CI: -4.20, 16.13]); (0.63 [95% CI: -12.38, 11.00]).

Interpretation: These results suggest that 3D-MOT training may offer therapeutic benefits by enhancing cognitive function and reducing daily life challenges in individuals with moderate to severe TBI.

**Disclosures:** I. Tucci: None. J. Morrison: None. T. Snowden: None. E. Skaug: None. I. Encina: None. K. Sternig: None. B.R. Christie: None.

**Poster**

**PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.06/H11

**Topic:** I.04. Executive Functions

**Title:** Cognitive Effects of Contact and Collision Sports in Youth

**Authors:** \*N. N. T. HETTIARACHCHI, V. VELARDE, N. LOCKWOOD, E. E. LEAVER, A. HICKS;

Psychology, Salisbury Univ., Salisbury, MD

**Abstract:** Chronic traumatic encephalopathy (CTE) and cognitive deficits result from repetitive head contact in athletes. This study compared cognitive and balance disparities among 36 college students (ages 18-23) divided into three groups: collision and contact sports (CLCN, n = 15), low-to-no-contact sports (LCON, n = 10), and controls (CTRL, n = 11). Data were collected using the NIH Toolbox Cognition Battery, Balance Error Scoring System (BESS), and self-report questionnaires. One-way ANOVA results showed that the CLCN group performed lower in expressive language, working memory, and processing speed compared to controls. Balance testing showed no differences on unstable surfaces, but the CLCN group performed better on stable surfaces. No significant differences emerged in self-reported concussion symptoms or depressive symptoms. These findings suggest that even low-level exposure to head contact in youth sports may affect cognitive function, highlighting the need for further research.

**Disclosures:** N.N.T. Hettiarachchi: None. V. Velarde: None. N. Lockwood: None. E.E. Leaver: None. A. Hicks: None.

## **Poster**

**PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.07/H12

**Topic:** D.04. Brain Injury and Trauma

**Support:** BRAIN Initiative UH3 Grant NS095554

**Title:** Identifying circuit modulation profiles for improving executive function in moderate to severe traumatic brain injury patients treated with deep brain stimulation (DBS)

**Authors:** \*M. P. HOOK<sup>1</sup>, J. CAGLE<sup>2</sup>, N. D. SCHIFF<sup>3</sup>, B. RUTT<sup>4</sup>, J. D. VICTOR<sup>6</sup>, J. L. BAKER<sup>10</sup>, X. ZOU<sup>11</sup>, S. IYENGAR<sup>11</sup>, M. SARANATHAN<sup>12</sup>, K. JAMISON<sup>7</sup>, A. KUCEYESKI<sup>8</sup>, S. A. SHAH<sup>9</sup>, J. M. HENDERSON<sup>5</sup>, C. R. BUTSON<sup>13</sup>;

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<sup>3</sup>Weill Cornell Med., New York City, NY; <sup>5</sup>Dept Neurosurgery, R 227, <sup>4</sup>Stanford Univ., Stanford, CA; <sup>6</sup>Feil Family Brain and Mind Res. Inst., <sup>8</sup>Radiology, <sup>9</sup>Dept. of Rehabil. Med., <sup>7</sup>Weill Cornell Med. Col., New York, NY; <sup>10</sup>BMRI, Cornell University: Weill Cornell Med. Col., New York,

NY; <sup>11</sup>Univ. of Pittsburgh, Pittsburgh, PA; <sup>12</sup>Radiology, Univ. of Massachusetts Chan Med. Sch., Amherst, MA; <sup>13</sup>Norman Fixel Inst. for Neurolog. Dis., Fixel Inst., Gainesville, FL

**Abstract:** We recently completed a BRAIN Initiative funded UH3 clinical trial that tested DBS for upregulating arousal in patients with moderate to severe traumatic brain injury (Schiff, Giacino, Butson, et al., Nature Medicine, 2023). The trial enrolled and implanted 5 subjects with DBS in the central lateral (CL) nucleus of thalamus, an important part of the frontal-striatal circuits that make up the mesocircuit arousal hypothesis. The results of the study showed that stimulation of the CL nucleus recruits these frontal-striatal projections for effective cognitive improvement. Our aim is to identify specific projections that correlate with improvement in executive function using connectomics analysis. We characterized connectivity in each subject by creating a whole brain parcellation atlas using the Human Connectome Project cortical atlas, the THOMAS thalamic atlas, the Harvard Ascending Arousal Atlas v2.0, and select subcortical segmentations from Freesurfer. These parcels were combined with whole brain tractography from MRtrix3 to create a biophysical head model. With these models, we simulated all stimulation settings that the participants received during the trial and calculated the connectivity of these effects to the regions in the parcellation atlas, identifying a distribution of “recruitment” profiles. These stimulation profiles were paired with clinical observations of these settings, categorized as cognitive, motor, and sensory outcomes with positive (+1), negative (-1), or neutral (0) responses. A statistical model was created using multinomial logistic regression. For feature selection, the Least Absolute Shrinkage and Selection Operator (LASSO) technique was used, coupled with a post-hoc correlation to offset penalty terms. Our preliminary results have shown that several regions from the mesocircuit, such as the Anterior Cingulate grouping, are positively correlated with a favorable cognitive response to stimulation. These stimulation-based profiles and corroborating statistical models allow for a finer detail of target and avoidance regions that could potentially be applied to future DBS candidates.

**Disclosures:** M.P. Hook: None. J. Cagle: None. N.D. Schiff: None. B. Rutt: None. J.D. Victor: None. J.L. Baker: None. X. Zou: None. S. Iyengar: None. M. Saranathan: None. K. Jamison: None. A. Kuceyeski: None. S.A. Shah: None. J.M. Henderson: None. C.R. Butson: None.

## **Poster**

### **PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.08/H13

**Topic:** D.04. Brain Injury and Trauma

**Support:** National Eye Institute R01EY030517  
National Institute of Neurological Disorders and Stroke R44NS095090  
National Eye Institute Core Grant for Vision Research P30 EY08098  
Eye and Ear Foundation of Pittsburgh, Research to Prevent Blindness, New York, N.Y. USA.



**Title:** Differences in fixational eye movements following concussion using an active fixation task

**Authors:** \*C. G. THOMPSON<sup>1</sup>, B. T. LEONARD<sup>2</sup>, M. ZHANG<sup>1</sup>, A. J. ZYNDA<sup>3</sup>, C. HOLLAND<sup>3</sup>, M. HIRSH<sup>3</sup>, C. K. SHEEHY<sup>4</sup>, A. KONTOS<sup>3</sup>, E. A. ROSSI<sup>1</sup>, R. JOHNSTON<sup>1</sup>; <sup>1</sup>Dept. of Ophthalmology, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; <sup>2</sup>Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA; <sup>3</sup>Dept. of Orthopaedic Surgery, Univ. of Pittsburgh, Pittsburgh, PA; <sup>4</sup>C. Light Technologies Inc., Boston, MA

**Abstract:** Fixational eye movements (FEMs) can be accurately measured using retinal image-based eye tracking, are associated with activity in brainstem regions that are vulnerable to force loading during a head impact and are significantly larger following concussion (Leonard et al., 2021, J. Vis.). However, research on FEMs following concussion has typically used passive fixation tasks that require participants to maintain their gaze on a static target. In this pilot study, we measured FEMs in adolescents with a recent concussion (N = 18,  $\leq 21$  days) and healthy controls (N = 21) while they performed an active fixation task. To perform this task, participants had to track the position of a Snellen E stimulus that was randomly displaced within the 5 x 5° imaging raster for 30s. The distance between each displacement ranged from -0.75 to 0.75°, and the time between each displacement ranged from 0.5 to 2s. Participants were asked to report the orientation of the stimulus, which was randomly changed on each displacement, to ensure that attention remained focused on the task. Eye movements were recorded using a tracking scanning laser ophthalmoscope (TSLO) and extracted from the TSLO images at 480Hz using strip-based image registration. To measure gaze accuracy, we computed the mean Euclidean distance between eye position and target position during each 30s epoch. Mean fixational saccade amplitude was also computed during periods of stable fixation between consecutive displacements of the Snellen E. Results showed that gaze accuracy did not differ significantly between concussion patients and controls ( $t(37) = -0.22929$ ,  $p = 0.81991$ ). However, concussion patients made larger fixational saccades than controls during periods of stable fixation between consecutive stimulus displacements ( $t(37) = -2.2502$ ,  $p = 0.30467$ ). These findings extend previous research on FEMs following concussion by demonstrating that deficits with FEMs may be limited to changes in the amplitude of fixational saccades that occur when gaze is maintained on a static object. Further research is needed to determine if the kinematics of the first saccade made after each stimulus displacement, and other types of FEMs (e.g., ocular drift) differ between concussion patients and controls on active fixation tasks that necessitate high visual acuity judgements.

**Disclosures:** C.G. Thompson: None. B.T. Leonard: None. M. Zhang: None. A.J. Zynda: None. C. Holland: None. M. Hirsh: None. C.K. Sheehy: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cofounder/CEO of C. Light Industries. A. Kontos: None. E.A. Rossi: None. R. Johnston: None.

**Poster**

**PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.09/H14

**Topic:** D.04. Brain Injury and Trauma

**Support:** Institute for Critical Technology and Applied Science (ICTAS)

**Title:** Relating head impacts to pupillary light reflex metrics and symptom reporting in collegiate rugby players

**Authors:** \*L. A. DUMA, M. CALHOUN, L. EDWARDS, K. METREY, S. ROWSON;  
Virginia Tech., Blacksburg, VA

**Abstract:** Concussions are a common sports-related injury, and repetitive concussions have been linked to long-term neurodegenerative processes. However, less is known about the cumulative effects of subconcussions: head impacts that do not result in a concussion diagnosis but induce mild concussion-like symptoms. In this study, we examined the relationship between subconcussive head impacts, pupillary light reflex metrics, and symptom reporting in fifteen male collegiate rugby players during eight games of 7s rugby. At the beginning of each day and after each game, players completed a symptom survey and a pupillary light reflex measurement. The total number of reported symptoms and the Symptom Severity Score (SSS), the sum of all symptom ratings, were calculated for each survey. Pupil measurements were taken with a PLR-3000 pupillometer (NeuroOptics). Videos of each game were taken from multiple angles, and head impacts were visually identified as changes in head trajectory due to direct head contact. Players wore instrumented mouthguards (HitIQ) for five of the eight games, and the recorded head acceleration data was used to verify the identified head impacts. For each player, the number of head impacts sustained in each game was counted, and the change in SSS, number of symptoms, and pupillometry metrics were calculated by subtracting baseline measurements from post-game measurements. There was no correlation between the number of head impacts and change in SSS, number of symptoms, or any pupillometry metric (SSS:  $r^2 = 0.02$ ,  $p = 0.24$ ; Number of symptoms:  $r^2 = 0.02$ ,  $p = 0.22$ ; Average constriction velocity:  $r^2 = 0.01$ ,  $p = 0.32$ ; Average dilation velocity:  $r^2 = 0.14$ ,  $p < 0.01$ ) (Figure 1). There was also no significant correlation between change in SSS and change in any pupillometry metric (Average constriction velocity:  $r^2 = 0.02$ ,  $p = 0.21$ ; Average dilation velocity:  $r^2 = 0.01$ ,  $p = 0.30$ ). The head impacts observed in this study, although frequent, were likely not severe enough to result in changes in the pupillary light reflex as observed in previous studies with concussed athletes.

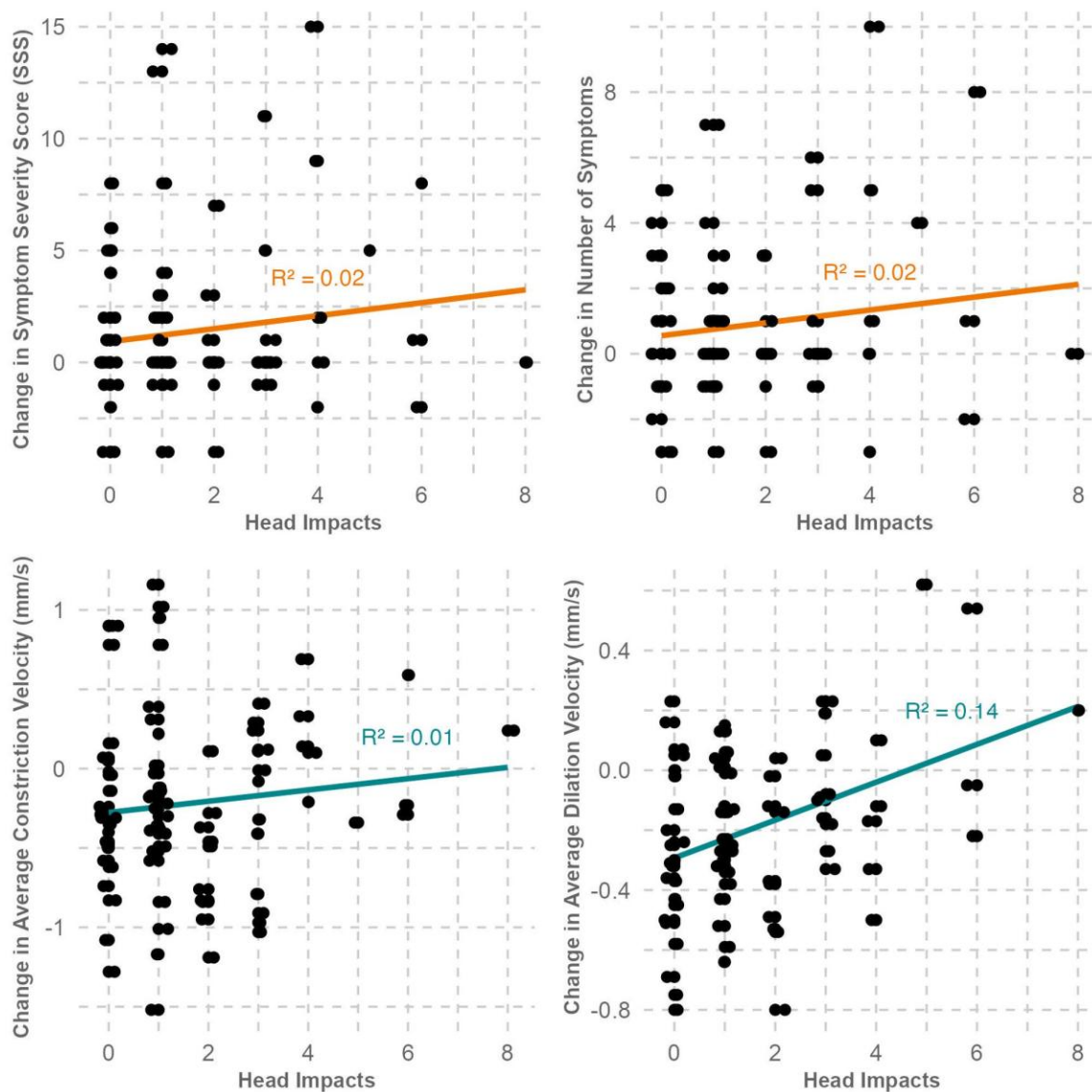


Figure 1: Correlation between head impacts and change in Symptom Severity Score (SSS), number of symptoms, average constriction velocity, and average dilation velocity after each game compared to baseline.

**Disclosures:** L.A. Duma: None. M. Calhoun: None. L. Edwards: None. K. Metrey: None. S. Rowson: None.

**Poster**

**PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.10/H15

**Topic:** D.04. Brain Injury and Trauma

**Title:** Parental awareness of concussions in youth sports: knowledge, attitudes, and observations of coaching response

**Authors:** \*A. ADAMI;  
Psychology, San Diego State Univ., San Diego, CA

**Abstract:** Background: Sports-related concussions (SRCs) are a type of mild traumatic brain injury (mTBI) caused from direct or indirect forces to the head that disrupts brain function. In the US, an estimated 3.8 million sports-related concussions occur each year posing significant short- and long-term health risks. While youth athletes are particularly vulnerable, the role of parental awareness and experiences with concussions detection and response remains underexplored in the US. This study examined parental awareness of concussion signs and symptoms, attitudes towards injury management on the field, and perceptions of coaching behavior in youth soccer. Methods: Primary research data was collected through a structured review of existing literature using PubMed, the CDC, and general google searches. Additionally, questionnaire data was collected from parents of youth athletes aged 10-17 across recreational and club teams. Results: Our preliminary results indicate that most parents had moderate to high awareness of common concussions symptoms (eg, headache, dizziness, confusion), but still need further education on concussions. When it came to parents scoring on a concussion attitude index, they also scored high. A small number of parents did report concerns about their child missing playing time due to the concussion protocol, potentially contributing to underreporting. Observational feedback on coaching behavior revealed wide variability in sideline recognition and protocol adherence across all competition levels. Conclusion: Little is known regarding the parental role in concussion reporting and care in youth athletes. Our findings suggest that general awareness is improving, but parental education on impact recognition and subtle symptoms needs to be explored further to better equip them as key stakeholders in youth athlete safety.

**Disclosures:** A. Adami: None.

**Poster**

**PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.11/H16

**Topic:** D.04. Brain Injury and Trauma

**Support:** USAMRAA under award number HT9425-24-1-0376

**Title:** From Diagnosis to Discharge: Evaluating Mild Traumatic Brain Injury Education Delivery in Emergency Settings

**Authors:** \*F. KHAN<sup>1</sup>, L. NELSON<sup>1,2</sup>, T. OKUSANYA<sup>3</sup>, C. BARRY<sup>1</sup>;

<sup>2</sup>Neurosci., <sup>1</sup>Med. Col. of Wisconsin, Milwaukee, WI; <sup>3</sup>Med. Col. of Wisconsin, MILWAUKEE, WI

**Abstract:** Introduction: Healthcare providers are encouraged to educate patients about mild traumatic brain injury (mTBI) immediately following injury. However, emergency department (ED) providers frequently demonstrate gaps in mTBI recognition and patient education. We present findings from the initial phase of our federally-funded Health Research Service award—a mixed methods investigation of ED clinicians' practices and perspectives regarding effective mTBI education delivery in the emergency setting. Materials and Methods: Our study encompassed seven EDs within the Froedtert Health System in Wisconsin, including one level 1 trauma center, two level 3 centers, and four community hospitals. From 505 eligible clinicians (physicians, residents, nurses, and advanced practice professionals), we collected 115 surveys assessing the acceptability, appropriateness, and feasibility of providing mTBI education. The survey incorporated the i-PARIHS (Promoting Action on Research Implementation in Health Services) planning tool and open-ended questions. Twenty-nine participants engaged in individual interviews (n=17) or focus groups (n=12) exploring clinical assessment workflows, education practices, and barriers to concussion education. Participants received \$50 compensation per activity. Data analysis utilized a deductive rapid qualitative approach through an iteratively updated "lightning report" synthesizing findings according to research questions and i-PARIHS domains. Results: Analysis revealed several key themes: provider knowledge gaps regarding TBI diagnostic criteria, variable diagnostic attitudes, and inconsistent discharge communication practices. These factors contribute to TBI underdiagnosis, inadequate patient education, and unnecessary ED returns. While patients generally understand the term "concussion," misconceptions persist. Educational challenges include patient factors (literacy levels, language barriers, support availability) and injury-related cognitive impairments. System-level barriers encompass time constraints, inadequate resources, electronic health record limitations, and unreliable follow-up care pathways. Conclusions: These findings illuminate the multifaceted challenges to effective ED-based mTBI patient education and will inform evidence-based interventions targeting identified barriers. Developing improved patient handouts and enhanced Epic SmartSets represents a promising approach to improve both patient education and provider efficiency in addressing mTBI in emergency settings.

**Disclosures:** F. Khan: None. L. Nelson: None. T. Okusanya: None. C. Barry: None.

## **Poster**

### **PSTR217: Brain Injury: Human Studies Cognition Circuits and Care**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR217.12/I1

**Topic:** D.04. Brain Injury and Trauma

**Title:** Concussion Care in Female Athletes: Survey and Literature Insights on Diagnosis, Treatment, and CTE Risk.

**Authors:** \*K. F. CROWLEY<sup>1</sup>, A. ADAMI<sup>2</sup>, G. MANTEK<sup>1</sup>, S. MCFARLIN<sup>3</sup>;

<sup>2</sup>Psychology, <sup>1</sup>San Diego State Univ., San Diego, CA; <sup>3</sup>San Diego State Univ., Coalinga, CA

**Abstract:** Female athletes remain underrepresented in chronic traumatic encephalopathy (CTE) research despite growing awareness of sports-related concussion (SRC) risks across youth, collegiate, and professional athletics. While increased attention has been paid to sex differences in concussion outcomes, gaps persist in how female athletes are diagnosed, treated, and monitored post-injury. This study aims to examine how female athletes in sports with high rates of head injuries (eg, soccer, volleyball, cheerleading, and gymnastics) are diagnosed, treated, and monitored following SRC. Using a cross-sectional survey design, we collected data from athletic trainers, healthcare professionals, and athletes to assess care immediately after the injury, return-to-play protocols, perceived inequities, and access to resources. We also conducted a literature review addressing sex differences in concussion diagnosis on the field. Our findings examine the current on-field practices and identify knowledge gaps related to concussion recovery in females and the risk for developing CTE. The earliest awareness of long-term impacts of head injuries was in the mid-1800s; the first official case of CTE was diagnosed in 2008, and it took 15 years for the first case of CTE to be diagnosed in a woman in 2023. Our study results emphasize the need to better understand current team culture and diagnostic approach with the needs of female athletes.

**Disclosures:** K.F. Crowley: None. A. Adami: None. G. Mantek: None. S. Mcfarlin: None.

## **Poster**

**PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.01/I2

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** Department of Defense (HT94252310700; SC220152)  
National Institute of Health (R21NS130241)  
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Department of Health (74247, 74244 and 55051)  
Ralph W. and Grace M. Showalter to L. Deng  
Ralph W. and Grace M. Showalter to X. Gao

**Title:** Repurposing Dexmedetomidine: early pharmacological hypothermia synergistically enhances neuroprotection, anti-inflammation, and functional recovery in rodent spinal cord injury

**Authors:** \*A. KHABBAZ, Y. MA, L. PRADHAN, S. CHAKRABORTY, Y. ZHANG, F. YUAN, A. E. GOWAN, E. D. HARRIS, X. GAO, L. DENG;  
Indiana Univ. Sch. of Med., Indianapolis, IN

**Abstract:** Spinal cord injury (SCI) causes motor, sensory, and autonomic dysfunction, posing a significant lifelong burden. Mechanical trauma initiates immediate tissue damage, followed by ischemia, excitotoxicity, and inflammation that exacerbate injury. Targeting these secondary mechanisms is a promising neuroprotective strategy. Systemic hypothermia mitigates such processes in preclinical models but is limited by a narrow therapeutic window and delayed clinical application. Furthermore, physically induced hypothermia provides only transient benefits. Therefore, combinatory strategies are needed. Dexmedetomidine (Dex), an FDA-approved sedative, has shown neuroprotective and anti-inflammatory effects in CNS injuries and, notably, also induces hypothermia. We hypothesized that Dex-induced hypothermia in acute SCI could enhance neuroprotection and anti-inflammation. In a T10 contusive SCI mouse model, a single Dex dose (100 µg/kg) IP administered within one hour post-injury induced moderate hypothermia (30-32°C) for up to 16 hours at room temperature (24.5°C). Dex-induced hypothermia reduced neuronal death, preserved white and gray matter, and increased spared neurons and axons. It also reduced macrophage infiltration and pro-inflammatory cytokines. Functionally, Dex improved long-term locomotion and urinary function (urine spot assay, urodynamics). Blocking hypothermia via heating pad significantly reduced Dex's protective effects, confirming hypothermia as a critical mediator. Notably, Dex-induced hypothermia outperformed conventional physical hypothermia. Inhibition of ERK signaling also diminished Dex's benefits, implicating ERK pathway involvement. In conclusion, Dex-induced hypothermia during acute SCI improves motor and urinary outcomes via synergistic neuroprotective and anti-inflammatory mechanisms. This novel use of Dex offers a promising early, on-site treatment strategy by enabling timely pharmacological hypothermia and overcoming logistical delays.

**Disclosures:** A. Khabbaz: None. Y. Ma: None. L. Pradhan: None. S. Chakraborty: None. Y. Zhang: None. F. Yuan: None. A.E. Gowan: None. E.D. Harris: None. X. gao: None. L. Deng: None.

## **Poster**

**PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.02/I3

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** NIH/NINDS R01 NS121336  
MU SCIDRP2024  
MizzouForward Initiative

**Title:** Neuroendocrine regulation of cardiovascular function after spinal cord injury

**Authors:** \*Z. QI<sup>1</sup>, F. KHODADADI MERICLE<sup>1</sup>, C. FOOTE<sup>1</sup>, R. BEN MUSA<sup>1</sup>, K. J. CUMMINGS<sup>2</sup>, E. M. HASSER<sup>2</sup>, S. HOU<sup>1</sup>;

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**Abstract:** Though the autonomic nervous system (ANS) plays a central role in cardiovascular control, hemodynamics is also regulated through hormone release, particularly by activation of the renin-angiotensin system (RAS). Following spinal cord injury (SCI), neural regulation of blood pressure is decreased while RAS activity is increased to maintain sufficient perfusion to important organs. It is unknown or controversial whether the aberrant elevation of hormonal regulation is involved in the development of autonomic dysreflexia, a potentially life-threatening condition, and baroreflex dysfunction in subjects with SCI. Using pharmacological intervention, we assessed the extent of neural or RAS contribution to resting hemodynamics and cardiovascular responses in rats with a 4<sup>th</sup> thoracic (T4) spinal cord transection. Sham-injured rats served as a control. A radio-telemetric transmitter was implanted in the abdominal cavity with a catheter sensor inserted into the descending aorta to monitor blood pressure and heart rate (HR). Administration of the ganglionic blocker Hexamethonium *i.p.* to inhibit neural control, or the angiotensin-converting enzyme 1 (ACE1) inhibitor Captopril and the AT<sub>1</sub>R antagonist Losartan to suppress the ACE/Ang II/AT<sub>1</sub>R axis, respectively, significantly reduced blood pressure and HR. In contrast, blocking the ACE2/Ang-(1-7)/MasR axis with either the MasR antagonist A779 or the ACE2 inhibitor MLN4760 did not alter resting hemodynamics. Meanwhile, administration of Hexamethonium, but not RAS antagonists, substantially attenuated the severity of colorectal distension (CRD)-induced autonomic dysreflexia. Subsequently, the arterial baroreflex was induced by continuously injecting the vasoconstrictor phenylephrine (PE, 0.2 mg/ml) followed by the vasodilator sodium nitroprusside (SNP, 0.06 mg/ml) at increasing rates to produce ramp changes in pressure. A sigmoidal logistic baroreflex curve was generated, and the gain of the baroreflex curve was quantified mathematically. Unexpectedly, SCI rats showed a steeper baroreflex curve and higher peak gain than shams, indicative of baroreflex hyperreflexia. Losartan, but not A779, flattened the curve and reduced the gain in SCI rats, implicating AT<sub>1</sub>R signaling in mediating the hyperreflexia response. Collectively, autonomic dysreflexia is mediated by neural but not RAS regulation. The baroreflex is hyperreflexive following SCI, which may create a permissive environment for CRD-induced hypertension by impairing compensatory mechanisms. The Ang II-AT<sub>1</sub>R pathway helps maintain resting blood pressure and facilitates exaggerated baroreflexes after SCI.

**Disclosures:** Z. Qi: None. F. Khodadadi Mericle: None. C. Foote: None. R. Ben Musa: None. K.J. Cummings: None. E.M. Hasser: None. S. Hou: None.

**Poster**

**PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM



**Program #/Poster #:** PSTR218.03/I4

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** NIH/NINDS R01 NS121336  
MU SCIDRP2024  
Mizzouforward Initiative

**Title:** Spinal D1D2 heteromer forms to mediate the involuntary bladder reflex after spinal cord injury

**Authors:** \*F. KHODADADI MERICLE<sup>1</sup>, C. FOOTE<sup>2</sup>, R. BEN MUSA<sup>3</sup>, Z. QI<sup>4</sup>, S. HOU<sup>5</sup>;  
<sup>1</sup>Univ. of Missouri - Columbia, Columbia, MO; <sup>2</sup>Dept. of Pathology and Anatom. Sci., Columbia, MO; <sup>3</sup>Biomed. science, Univ. of Missouri, Columbia, MO; <sup>4</sup>Univ. of Missouri, Columbia, MO; <sup>5</sup>Dalton Cardiovasc. Res. Ctr., Univ. of Missouri-Columbia, Columbia, MO

**Abstract:** Micturition dysfunction occurs after spinal cord injury (SCI). Though voluntary bladder activity is immediately ablated in response to trauma, a segmental micturition reflex can gradually be established to facilitate involuntary voiding due to newly formed spinal circuits via intraspinal plasticity. We previously disclosed that spinal dopaminergic machinery emerges to regulate partially recovered bladder function following SCI. However, this neuronal mechanism remains unclear, as dopamine effects on urinary performance could not be simply interpreted as activation of D1 and/or D2 receptors. Based on preliminary data, we hypothesized that a D1-D2 receptor complex forms in the spinal cord to mediate spontaneous urination after SCI. Herein, we tested this hypothesis in the micturition reflex. Adult female rats underwent complete transection at the 10th thoracic (T10) spinal cord. After 3-4 weeks, a cohort of rats was sacrificed and ~0.5 cm of the L6/S1 spinal tissue, where dopamine neurons controlling the bladder and EUS are located, was dissected for D1-D2 co-immunoprecipitation. Immunoprecipitation of D2 (capture/bait antibody =  $\alpha$ D2) resulted in copurification of D1 (western-blot primary antibody =  $\alpha$ D1). Quantification of the western-blot bands (Image Lab Software, Bio-Rad) indicated a significant increase in D2 receptor in the injured cord compared to naïve rats. In parallel, anesthetized animals received bladder catheterization and electrode insertion into the external urethral sphincter (EUS). Following lumbar laminectomy, an intrathecal (i.t.) catheter was inserted rostrally to the L6/S1 spinal level for drug delivery. Then, conscious rats were restrained for continuous bladder cystometrograms (CMG) and EUS electromyography (EMG) recordings. A series of doses (4, 40, and 400  $\mu$ g/kg, 10  $\mu$ L) of the TAT-D1 peptide, an antagonist specific to D1-D2 heteromers, was i.t. administered. The high dose induced increased volume thresholds (VT) and prolonged voiding intervals (VI), indicating an inhibitory effect on voiding. Furthermore, pharmacological stimulation of D1-D2 heteromers with a combination of SKF 38393 (1 mg/kg, 10  $\mu$ L), a D1 receptor agonist, and Quinpirole (0.03 mg/kg, 10  $\mu$ L), a D2 receptor agonist, enhanced voiding volume (VV) and reduced VI, suggesting improved voiding capability. Subsequently, injection of TAT-D1 (400  $\mu$ g/kg, 10  $\mu$ L) eliminated these effects. The results identified increased presence of D1-D2 heteromers in the injured spinal cord and their role in regulating the involuntary bladder reflex. Ultimately, activation of this receptor heteromer may serve as a therapeutic target to improve voiding capability after SCI.

**Disclosures:** F. Khodadadi Mericle: None. C. Foote: None. R. Ben Musa: None. Z. Qi: None. S. Hou: None.

**Poster**

**PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.04/I5

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** PICT 2021 N° 348 from Argentine Ministry of Science and Technology  
PIP 2022–2024 N° 334 from the National Research Council of Argentina

**Title:** Phytocannabinoids attenuate neuroinflammatory responses and promote functional locomotor recovery after spinal cord injury

**Authors:** \*J. DEL CORE, A. DE NICOLA, M. LABOMBARDA;  
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**Abstract:** Neuroinflammation is involved in both secondary damage and functional deficits after traumatic spinal cord injury (SCI), so its regulation represents a therapeutic target. In this regard, Tetrahydrocannabinol (THC) and Cannabidiol (CBD), the main phytocannabinoids of Cannabis Sativa, emerge as anti-inflammatory molecules. The objective of this study was to evaluate the effects of cannabis sativa extract (CAN) on neuroinflammation and locomotor recovery in a rat model of SCI. The extract is composed of an equimolar concentration of THC: CBD. SCI rats received an oromucosal dose (20mg/kg/day) during 15 days post-injury (dpi), and they were sacrificed in the acute (6 hours post-injury -hpi- and 3 dpi), sub-acute (7 dpi) and chronic phases (60 dpi). By Real Time RT-PCR, pro-inflammatory (TNF $\alpha$ , IL-1 $\beta$ , IL-6) and anti-inflammatory (TGF $\beta$ , ARG-1, MRC) markers were determined during the acute and sub-acute phases. After SCI, the expression of all pro-inflammatory markers was increased compared to sham rats ( $p < 0.001$ , ANOVA one-way), while the expression of anti-inflammatory molecules remained as sham values. Unlike, CAN treatment decreased the expression of pro-inflammatory molecules ( $p < 0.05$  vs SCI rats, ANOVA one-way) and increased the expression of anti-inflammatory ones ( $p < 0.01$  vs SCI rats, ANOVA one-way). Moreover, confocal analysis of a double immunohistochemistry (Iba-1 and ARG-1) showed that CAN treatment increased the number of microglial cells (Iba-1+ cells) that express ARG-1 (an anti-inflammatory marker,  $p < 0.05$  vs SCI rats, ANOVA one-way). Moreover, at the chronic phase, the microglial cell number was also decreased by CAN treatment ( $p < 0.01$  vs SCI rats, ANOVA one-way). Finally, we evaluate functional recovery at the chronic phase. BBB analysis showed that CAN improved locomotor recovery from 7 dpi ( $p < 0.05$ , ANOVA one-way). Rotarod analysis showed that CAN treatment increases the latency to fall compared to SCI rats ( $p < 0.05$ , ANOVA one-way). Regarding the horizontal ladder, SCI rats increased the number of hindlimb foot misplacements compared to sham rats ( $p < 0.05$ , ANOVA one-way), while CAN treatment reduced the value of this parameter ( $p < 0.05$  vs SCI rats, ANOVA one-way). These results suggest that THC and CBD offer a

promising perspective in reducing acute neuroinflammation, promoting functional recovery after SCI.

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**Poster**

**PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.05/I6

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** NIH Grant 1R01NS14285-01

**Title:** Blood pressure augmentation to improve intraspinal blood flow following cervical spinal cord injury in rats

**Authors:** \*D. E. JENSEN<sup>1,2</sup>, A. A. ODARENKO<sup>1,2</sup>, L. N. CATES<sup>1,2</sup>, Z. Z. KHAING<sup>1,2</sup>;  
<sup>1</sup>Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA; <sup>2</sup>Dept. of Anatom. Sci. and Neurobio., Univ. of Louisville, Louisville, KY

**Abstract:** Blood pressure maintenance is a common clinically used strategy for acute spinal cord injury (SCI) management. Maintenance of mean arterial pressure (MAP) between 85 - 90 mmHg is used to limit loss of blood flow to the spinal cord associated with the injury. However, it is unclear whether maintaining MAP within the recommended range results in better intraspinal blood flow. Here, we aim to use a novel ultrafast contrast-enhanced ultrasound (CEUS) to observe vascular changes and evaluate the therapeutic potential of elevated acute MAP via norepinephrine (NE) administration. Mature female Long Evans rats were anesthetized and a femoral catheter was inserted for real-time systolic and diastolic pressure monitoring. Each rat underwent a three-level laminectomy, followed by a moderate cervical (C5) contusion injury and a subsequent subcutaneous injection of either saline control (0.9% NaCl, N=4) or NE treatment (0.5 mg/kg, N=6) immediately after injury. CEUS imaging was performed at three time points: baseline (pre-injury), acutely post-injury, and at 4 hours post-injury (hpi). MAP was measured pre-injury and up to 5 hpi. As expected, after cervical SCI, there was a rapid decline in MAP (87 to 46 mmHg) which remained below baseline for at least 60 minutes post-SCI. Treatment with NE restored blood pressure to baseline levels quicker (27 min;  $p < 0.01$ , mixed-effects ANOVA) and elevated MAP to a greater extent (+47 mmHg above baseline;  $p < 0.0001$ , t-test) compared to control animals. At 4 hpi, NE-induced MAP elevation resulted in measurable hemodynamic changes via CEUS imaging, including a reduced perfusion deficit volume and a smaller medial-lateral extent of perfusion deficit. These data demonstrate a first direct connection between bolstered MAP after injury and improved intraspinal blood flow and tissue perfusion. Future studies will adopt a longitudinal approach to investigate the enduring impact of acute MAP augmentation on intraspinal hemodynamics. Novel intravital CEUS imaging provides direct

evidence of improved spinal tissue perfusion by maintaining MAP and this may limit secondary damage following acute SCI ultimately reducing functional loss to patients with cervical SCI.

**Disclosures:** D.E. Jensen: None. A.A. Odarenko: None. L.N. Cates: None. Z.Z. Khaing: None.

## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.06/I7

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** Craig H. Neilsen foundation, #1165231

**Title:** Selective inhibition of Fatty Acid Binding Protein 5 (FABP5) reduces nociceptors' excitability and chronic neuropathic pain in a mouse model of spinal cord injury.

**Authors:** \*J. GUPTA<sup>1</sup>, K. GUNARATNA<sup>2</sup>, H. LIU<sup>2</sup>, E. H. SIPPLE<sup>1</sup>, M. KACZOCHA<sup>2</sup>, M. PUOPOLO<sup>2</sup>;

<sup>1</sup>Stony Brook Univ., Stony Brook, NY; <sup>2</sup>Dept. of Anesthesiol., Stony Brook Med., Stony Brook, NY

**Abstract:** Up to 60-70% of spinal cord injury (SCI) patients suffer from lifelong neuropathic pain. Anticonvulsant and antidepressant drugs are used as the first analgesic choice to treat SCI-induced neuropathic pain (SCI-NP), but patients report unsatisfactory pain relief. SCI-NP may become lifelong and therapeutically intractable, leading to a severe decline in quality of life. Hyperexcitable and spontaneously active nociceptors have been suggested to play a primary role in the development of SCI-induced neuropathic pain (SCI-NP). Previous work from our laboratory showed that SCI results in increased activity of T-type calcium channels which drive nociceptors' hyperexcitability and promotes the development and persistence of SCI-NP. Fatty acid binding protein 5 (FABP5) is an intracellular carrier for endocannabinoids and related lipids that mediates anandamide (AEA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) transport to fatty acid amide hydrolase (FAAH) for inactivation. AEA has been shown to directly inhibit T-type channels independently of CB receptors. This suggests that inhibition of FABP5 (with subsequent increase in AEA levels) may provide a strategy to reduce nociceptors' hyperexcitability and SCI-NP. *Methods.* SCI was performed in mice by a midline spinal cord contusion at T10 (50-60 kilodynes). The mechanical allodynia was measured with the von Frey filaments; spontaneous pain was measured with the conditioned place preference (CPP) paradigm. The action potential clamp technique was used in dissociated dorsal root ganglia (DRG) neurons isolated from SCI and sham mice to measure the T-type calcium current during the interspike interval. *Results.* In wild type mice, the 50% mechanical threshold dropped from 1.51±0.14 g (pre-injury) to 1.06±0.13 g (post-SCI) and to 1.11±0.17 g following vehicle injection. ART26.12 (40 mg/kg, an FABP5 inhibitor) increased the 50% mechanical threshold to

1.70±0.28 g (n=6) at 1-hour post-injection. When tested with the CPP paradigm to measure spontaneous pain, wild type mice showed an increase in the ART26.12 paired chamber of 42±22 sec and a decrease in the vehicle-paired chamber of -5±14 sec (n=6). The total interspike calcium charge and the interspike T-type calcium charge were reduced from 75±13 fC/pF and 45±13 fC/pF in control to 47±10 fC/pF and 26±9 fC/pF (n=11) in the presence of 5 µM ART26.12, consistent with reduced nociceptors' excitability. Taken together, our data suggest that inhibition of FABP5 with ART26.12 reduces T-type calcium current and nociceptors' hyperexcitability, mechanical hypersensitivity, and spontaneous pain in mice subjected to SCI. Data are reported as mean±SEM.

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## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.07/I8

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** NRF RS-2024-00419269  
RS-2023-00254156  
MOTIE P246800201

**Title:** Optimal Dose of Pregabalin Enhances Functional Recovery After Spinal Cord Injury

**Authors:** \***D. KIM**<sup>1</sup>, L. LIU<sup>1</sup>, Y.-J. KIM<sup>3</sup>, J. HYUN<sup>2</sup>;

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**Abstract:** Spinal cord injury (SCI) causes profound and often irreversible impairments in motor, sensory, and autonomic function, resulting from both the initial trauma and a cascade of secondary injury mechanisms. In particular, glutamate excitotoxicity, calcium influx, oxidative stress, mitochondrial dysfunction, blood-spinal cord barrier disruption, sustained neuroinflammation, and inhibitory glial scar formation create a hostile environment that limits intrinsic neuronal repair and long-term recovery. Pregabalin (PGB), a gabapentinoid that binds to the  $\alpha 2\delta$  subunit of voltage-gated calcium channels, is widely prescribed for neuropathic pain due to its ability to modulate neuronal excitability. Recent evidence suggests that early administration of gabapentinoids after SCI may also support motor recovery by influencing synaptic plasticity and neuroinflammatory processes. However, the therapeutic mechanisms,

optimal dosing, and regenerative potential of PGB remain incompletely defined. In this study, we systematically evaluated the efficacy of PGB in promoting functional recovery after SCI using both in vitro and in vivo models, including dose-response analysis and transcriptomic profiling. In vitro, primary cortical neurons were cultured and injured using hydrogen peroxide to simulate oxidative stress. PGB treatment (5- 500  $\mu$ M) enhanced cell viability, neurite outgrowth, and branching, with the strongest effect at 5  $\mu$ M. In vivo, moderate thoracic contusion injuries were induced in rats, and PGB (5-120 mg/kg/day) was administered intraperitoneally, and functional outcomes were assessed using the Basso, Beattie, Bresnahan scale and horizontal ladder test. We found that the 5 mg/kg group showed the most substantial and consistent improvements in motor function up to 8 weeks post-injury. Histological analyses revealed reduced lesion volume, preserved myelin integrity, and diminished activation of microglia and macrophages in PGB-treated spinal cords. Transcriptomic profiling of spinal tissues showed that PGB broadly suppressed inflammatory and excitotoxic gene expression while upregulating pathways associated with neuronal regeneration and repair. In conclusion, these findings demonstrate that early, low-dose PGB treatment not only enhances functional recovery but also modulates key biological processes to foster a pro-regenerative microenvironment. This study refines our understanding of PGB's therapeutic profile and supports its potential repositioning as a dual-action, clinically translatable intervention for improving outcomes following SCI.

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## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.08/19

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** NeOnc Technologies, Inc.

**Title:** Cellular uptake of Cy5-miR133b/NEO100 in acute and subacute cervical spinal cord lesions after intranasal administration in a mouse model of contusive injury

**Authors:** \*C. A. DANILOV<sup>1</sup>, J. Y. H. YU<sup>3</sup>, L. BERNAL<sup>2</sup>, T. THEIN<sup>2</sup>, T. C. CHEN<sup>4</sup>;  
<sup>1</sup>Neurolog. Surgery, <sup>2</sup>USC, Los Angeles, CA; <sup>3</sup>Neurolog. Surgery, Keck Sch. of Med. at the Univ. of Southern California, Los Angeles, CA; <sup>4</sup>LAC & USC Med. Ctr., Los Angeles, CA

**Abstract:** MicroRNA133b (miR133b) is a short non-coding, post-transcriptional regulatory molecule that targets the extracellular matrix microenvironment to reduce fibrosis following neurotrauma. Our previous studies have demonstrated that intranasal co-administration of miR133b with NEO100, a purified version of perillyl alcohol, improves motor recovery in a mouse model of acute spinal cord injury (SCI) when administered 24 hours after the injury. However, the cellular specificity of miR133b during the acute and subacute phases of scar formation remains to be determined. Here, we examined the distribution of miR133b/NEO100

intranasally in acute and subacute cervical cord lesions by labeling miR133b with the fluorophore Cyanine 5 (Cy5). Mice were divided into sham, acute, and subacute injury groups. The sham group received only laminectomy and intranasal Cy5-miR133b with/without NEO100. The acute and subacute injury groups received moderate unilateral contusions at the cervical 5<sup>th</sup> (C5) level using an IH impactor. The acute injury group received Cy5-miR133b with/without NEO100 at 24 hours post-SCI, and the subacute group received either formulation at 96 hours post-SCI. All mice were euthanized 24 hours after therapy. Sections of the cervical spinal cord were immunolabeled for neurons (Neu-N), astrocytes (GFAP), pericytes (PDGFR $\beta$ ), and myelin (MBP). Intranasally administered Cy5-miR133b reached the cervical cord in all groups, as visualized by fluorescence microscopy. Cy5-miR133b predominantly co-localized with neurons within the gray matter, and the concentration was higher when co-delivered with NEO100. Less distribution of Cy5-miR was found in the white matter across all groups. In the acute and subacute injury groups, Cy5-miR133b was largely concentrated in the lesion core. Although activated astrocytes were present in the injury groups, there was no co-localization with Cy5-miR133b in either the acute or subacute groups. Notably, pericytes were only present in the subacute group and strongly co-localized with Cy5-miR133b. In summary, intranasal administration of Cy5-miR133b reaches the gray matter of the cervical spinal cord within 24 hours of delivery, and the uptake is enhanced by NEO100. The presence of Cy5-miR133b is pronounced in the lesion core and co-localizes with surrounding pericytes, but not with astrocytes, during the subacute period. The unique cellular specificity of Cy5-miR133b for pericytes suggests that the mechanism targets fibrosis rather than gliosis. The delayed recruitment of pericytes following a traumatic spinal cord injury supports that the optimal timing of miR133b therapy may be during the subacute phase.

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## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.09/I10

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** K2509181/Korea University  
NRF-2022R1F1A1073548/Korea Science and Engineering Foundation (KOSEF), funded by the Ministry of Science and ICT

**Title:** Astrocytic inducible nitric oxide synthase upregulation contributes to chronic below-level neuropathic pain following spinal cord injury

**Authors:** Y. KIM, J. BAEK, \*Y. W. YOON;  
Korea Univ. Col. of Med., Seoul, Korea, Republic of

**Abstract:** Spinal cord injury (SCI) leads to persistent inflammation, contributing to chronic neuropathic pain. However, current treatments show limited efficacy. Three types of nitric oxide synthase (NOS) play different roles in inflammation and neuronal hyperexcitation. Therefore, this study aimed to determine the predominant NOS subtype involved in neuropathic pain after spinal contusion. We investigated the effects of intrathecal NOS inhibitors on mechanical sensitivity following a moderate spinal contusion injury in male Sprague-Dawley rats. These NOS inhibitors were N(G)-nitro-L-arginine methyl ester hydrochloride (L-NAME; non-selective NOS inhibitor), 1400W (iNOS inhibitor), N $\omega$ -propyl-L-arginine hydrochloride (NPLA; nNOS inhibitor) and N5-(1-iminoethyl)-L-ornithine (L-NIO; eNOS inhibitor). Additionally, we analysed protein expression and cellular localisation of spinal NOS subtypes in rats that underwent SCI or sham procedures. Treatment with L-NAME significantly reduced paw withdrawal threshold in a dose-dependent manner, although motor deficits appeared at the highest dose (30  $\mu$ M), while 1400W effectively alleviated mechanical hypersensitivity without motor side effects. NPLA showed limited efficacy, and L-NIO had no effect. Protein expression of iNOS increased two-fold in the L4-5 spinal segment of SCI rats compared with sham controls. After SCI, iNOS-immunoreactivity colocalized with GFAP in the superficial laminae of the L4-5 spinal segment. Treatment with 1400W reduced the hyper-reactivity of both iNOS and GFAP. These findings indicate that iNOS plays a significant role in below-level neuropathic pain following thoracic spinal cord contusion in rats. Specific blockade of iNOS activity may have potential as a therapeutic intervention for spinal contusion-induced neuropathic pain with reduced risk of side effects.

**Disclosures:** Y. Kim: None. J. Baek: None. Y.W. Yoon: None.

## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.10/I11

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** New Jersey Commission on Spinal Cord Research Postdoctoral Fellowship Grant CSCR25FEL002

**Title:** Local injection of a biodegradable hydrogel graft incorporating anti-inflammatory nanosheets and neurogenic embryonic neural progenitor cells for functional recovery following spinal cord injury

**Authors:** \*W. KO;

Rutgers University/Department of Chem. and Chem. Biol., Piscataway, NJ

**Abstract:** Traumatic spinal cord injury (SCI) is a debilitating condition caused by severe damage to the central nervous system, often resulting in prolonged motor dysfunction due to the secondary inflammatory response. To overcome this challenge, we engineered a biodegradable



hybrid hydrogel graft integrating anti-inflammatory manganese dioxide (MnO<sub>2</sub>) nanosheets with embryonic spinal cord-derived neural progenitor cell (eNPC) spheroids possessing neuronal differentiation potential. Our findings revealed that MnO<sub>2</sub> nanosheets effectively suppressed inflammatory cytokine production in lipopolysaccharide (LPS)-stimulated macrophages. Moreover, in a mouse model of SCI, transplantation of eNPCs via the hybrid graft led to significantly improved motor function recovery compared to control groups. These results highlight the therapeutic potential of this hybrid graft as a promising intervention for SCI.

**Disclosures:** W. Ko: None.

## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.11/I12

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** Craig H Neilsen Foundation Grant 1000927.

**Title:** Targeting the brain-spinal cord axis and local processes to protect against secondary damage following spinal cord injury (SCI)

**Authors:** \*N. KOBAYASHI, C. T. PHINNEY, J. W. GRAU;  
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**Abstract:** Noxious stimulation a day after a thoracic spinal cord injury is associated with increased hemorrhage at the site of injury and impaired long-term recovery in rats. Disrupting communication between the brain and spinal cord via a transection at an upper thoracic level (T2), attenuates this pain-induced hemorrhage. Blocking communication with the brain by infusing lidocaine rostral to injury also has a protective effect (Davis et al., 2020, J Neurotrauma, 37). However, regional application of an anesthetic (lidocaine), administered via a lumbar puncture targeting the cauda equina, also blocks the adverse effect of nociceptive stimulation (Turtle, 2017, J Neurotrauma, 34). The existing literature suggests that both systemic and local processes are driving secondary injury even at a day post-injury. The present study aims to expand on this to explore whether physically and pharmacologically cutting the brain-spinal cord crosstalk immediately after injury can have protective effects. First, a transection or sham injury was given before or after a moderate thoracic (T11-12) contusion injury. Fresh tissue was collected 24 hrs following injury to be assayed for hemorrhage. We then explored the pharmacological side - would application of an anesthetic have a protective effect when initiated soon after injury. To assure sustained action, a longer acting anesthetic (bupivacaine) was used, administered via a catheter implanted after rats received a contusion injury. A pilot experiment verified that infusion of bupivacaine (0.75%) into the cauda equina inhibited locomotor function and tail withdrawal from a noxious thermal stimulus for 90-120 min. We then assessed the effect of bupivacaine applied 4.5 cm rostral to injury or into the cauda equina, with the first injection

given 5 min after surgery. Separate groups then received 0, 1, 3, or 7 additional injections at 90 min intervals to maintain the anesthesia for 1.5, 3, 6, or 12 hrs. A day after injury, locomotor function was assessed using the converted BBB scale and a 1 cm region surrounding the injured spinal cord region was taken and assayed for hemorrhage. Animals that received a transection prior to, but not after injury had less hemorrhage at the site of injury. Animals that received bupivacaine rostral to the site of injury for 3-12 hrs exhibited improved locomotor performance and less hemorrhage at the site of injury. Epidural application to bupivacaine only improved locomotor function for the 3 hr administration.

**Disclosures:** N. Kobayashi: None. C.T. Phinney: None. J.W. Grau: None.

## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.12/J1

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** Neilsen Foundation Grant #1000927

**Title:** Evaluating the Protective Effect of Midazolam on Pain-Induced Hemorrhage and Locomotor Impairment After Spinal Cord Injury

**Authors:** \*J. ABRAHAM<sup>1</sup>, C. T. PHINNEY<sup>1</sup>, V. BALENTINE<sup>1</sup>, N. KOBAYASHI<sup>1</sup>, J. DAVIS<sup>2</sup>, J. W. GRAU<sup>1</sup>;

<sup>1</sup>Psychology, Texas A&M Univ., College Station, TX; <sup>2</sup>Neurosurg., UCSF, San Francisco, CA

**Abstract:** Spinal cord injury (SCI) can trigger secondary damage exacerbated by nociceptive input. Prior work has demonstrated that peripheral nociceptive stimulation after a contusion injury increases tissue loss and impairs recovery (Turtle, 2017, *J Neurotrauma*, 34, 1200). Notably, general anesthesia using isoflurane, and central depressants like pentobarbital, administered prior to stimulation can block this effect. It is currently unclear whether the protective effect is linked to the induction of a coma-like state. In past studies (Hook, 2007, *Beh Brain Res*, 179, 281), we addressed this issue by evaluating the effect of the analgesic morphine. Morphine had no effect. To examine whether inducing a dissociative state has a protective effect, we tested the effect of ketamine (100 mg/kg). It too did not attenuate pain-induced hemorrhage in contused rats. The current project extends this work to examine whether the benzodiazepine midazolam, which enhances GABA-A receptor function, can attenuate pain-induced hemorrhage following SCI. Male rats received a moderate contusion injury at thoracic level T12. After 24 hours, animals were pretreated with midazolam (1 mg/kg, i.p.) or its vehicle prior to nociceptive tail shock. Three hours post-stimulation, a 1-cm section of spinal tissue centered at the lesion site was extracted. Preliminary results suggest the drug attenuated the immediate effect of pain on locomotor function, but this effect waned over time. Further work is being conducted to determine whether a higher dosage, that produces a more uniform state of sedation across

animals, has a lasting protective effect. Positive results would suggest an avenue for clinical treatment that could attenuate the adverse effect of pain from polytrauma without inducing a state of general anesthesia.

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## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.13/J2

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** Craig H Neilsen Foundation #1176717

**Title:** Targeting Nav 1.7 and 1.8 to attenuate neuropathic pain and improve locomotion after SCI

**Authors:** Z. F. HERRIMAN<sup>1</sup>, S. PARVIN<sup>1</sup>, \*S. M. GARRAWAY<sup>2</sup>;

<sup>1</sup>Cell Biol., <sup>2</sup>Emory Univ. Sch. of Med., Atlanta, GA

**Abstract:** Spinal cord injury (SCI) causes many devastating effects that can have lasting impacts on individuals' quality of life. Chronic neuropathic pain is a common occurrence after SCI that remains unresolved, mainly because the underlying neural mechanisms are not fully known. Voltage-gated sodium channels (Navs) are important for establishing neuronal excitability. However, several Nav subtypes: Nav 1.7, 1.8 and 1.9, are uniquely positioned on nociceptors, making them important targets for pain (reviewed by Jang & Garraway, *Neurobiology of Pain*, 2024). Although studies have demonstrated changes in the expression and function of Navs in inflammatory and injury-induced pain, their role in neuropathic pain and locomotor dysfunction after SCI has been minimally studied.

We previously showed that events such as nociceptor hyperactivity immediately after SCI are critical to the development and long-term expression of pain responses (e.g. Garraway et al. *Pain* 2014; Martin et al. *J. Neurotrauma*, 2019). Here, we proposed aberrant Nav signaling acutely after SCI also contributes to pain hypersensitivity and locomotor deficits. Therefore, we investigated the effect of Nav inhibition on the development of reflexive and operant pain, and hindlimb locomotor function after SCI. PF-04856264 and A-803467 (Nav 1.7 and 1.8 inhibitors, respectively) were administered to adult mice for 7 days beginning 1 day post SCI (dps; 10 mg/kg, intraperitoneally). Behavioral tests were done before SCI (baseline) and up to 35 dps. The results showed that PF-04856264, the Nav 1.7 blocker, reduced the duration of mechanical hypersensitivity on the von Frey test. Compared to baseline, mice exhibited a significant decrease in withdrawal threshold 7 and 21 dps ( $p < .01$ ) but not 35 dps ( $n=6$ ). SCI mice treated with saline (Sal) were hypersensitive at all 3 timepoints compared to baseline ( $p < .05$  to  $p < .01$ ;  $n = 6$ ). PF-04856264 also completely blocked the development of operant pain at 14 dps compared to SCI-Sal mice. Lastly, PF-04856264-treated mice had slightly improved hindlimb

locomotion on the Basso Mouse Scale. None of these effects were seen in mice treated with A-803467, the Nav 1.8 blocker, which typically resembled SCI-Sal mice. qRT-PCR revealed that the Nav inhibitors did not influence mRNA levels of the pro-inflammatory cytokines, IL-1 $\beta$  and TNF $\alpha$ , in the injured spinal cord at >35 dps. Altogether, these results suggest that maladaptive plasticity acutely after SCI that produces pain and impairs locomotion, engages Nav 1.7 dependent mechanisms. Further exploration of Nav 1.7 signaling, presumably in nociceptors, to determine their exact role in neuropathic pain after SCI is warranted.

**Disclosures:** Z.F. Herriman: None. S. Parvin: None. S.M. Garraway: None.

## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.14/J3

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** NIH Grant R01-NS110385

**Title:** Dysregulation of EphB2 modulation of glutamatergic neurotransmission in a mouse model of neuropathic pain induced by cervical SCI.

**Authors:** \*L. NGUYEN<sup>1</sup>, M. L. COVARRUBIAS<sup>2</sup>, A. C. LEPORE<sup>1</sup>, D. JAFFE<sup>1</sup>;

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**Abstract:** Neuropathic pain (NP) affects a majority of spinal cord injury (SCI) survivors, yet treatments remain inadequate. NP often results from pathological sensitization, a state characterized by heightened responsiveness of pain circuitry neurons. A critical mechanism underlying this process is enhanced activity of post-synaptic excitatory glutamate receptors on dorsal horn (DH) projection neurons in response to inputs from primary sensory afferents. Unfortunately, direct targeting of glutamate receptors failed clinically due to detrimental adverse effects. Synaptic EphB2 (erythropoietin-producing hepatocellular carcinoma B2) receptors have emerged as potential therapeutic targets because they are major regulators of ionotropic glutamatergic signaling in mature excitatory synapses. Ongoing studies have shown that, following cervical SCI in mice, EphB2 expression and signaling are robustly increased in the nociceptive-specific superficial DH of the spinal cord. Remarkably, EphB2 knock out (KO) rescues already-established mechanical hypersensitivity in SCI mice. However, it is not known how SCI affects glutamatergic signaling between primary sensory afferents and second-order projections neurons and how EphB2 targeting may restore normal glutamatergic neurotransmission. We hypothesize that cervical SCI dysregulates EphB2's modulation of synaptic NMDA and AMPA receptors and the intrinsic excitability of projection neurons in lamina I. To directly test this hypothesis, I have 1) implemented and optimized transverse cervical spinal cord slices (C7-C8) from adult mice (2-4 months), which are suitable for patch-

clamp analysis of DH projection neurons and 2) retrogradely labeled spinoparabrachial projections neurons. Early recordings from lamina I neurons in cervical slices from control mice demonstrate robust passive and active membrane properties, with mean resting membrane potential of -72.13 mV ( $\pm$  5.15), membrane capacitance of 18.86 pF ( $\pm$  3.38), input resistance of 1.47 G $\Omega$  ( $\pm$  0.87), rheo base of 83.75 mV ( $\pm$  21.79), and single spike and phasic firing patterns. Our work was supported by the NINDS (R01NS110385 to ACL and MC; R01NS079702 to ACL).

**Disclosures:** L. Nguyen: None. M.L. Covarrubias: None. A.C. Lepore: None. D. Jaffe: None.

## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.15/J4

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** Office of Research and Graduate Studies, Central Michigan University  
Program in Neuroscience, Central Michigan University  
College of Medicine, Central Michigan University  
The John G. Kulhavi Professorship in Neuroscience, Central Michigan University  
The E. Malcolm Field and Gary Leo Dunbar Endowed Chair in Neuroscience, Central Michigan University

**Title:** Systemic versus Intrathecal Delivery of Etanercept and Methylprednisolone in Modulating Functional Recovery in Experimental Spinal Cord Injury

**Authors:** \*L. G. GARMO<sup>1</sup>, J. HUGHES<sup>1</sup>, S. OSBORN<sup>1</sup>, E. HOCK<sup>1</sup>, E. DARRAGH<sup>1</sup>, G. TAVI<sup>1</sup>, D. DOYLE<sup>1</sup>, J. ROSSIGNOL<sup>2</sup>, G. L. DUNBAR, Sr.<sup>3</sup>;

<sup>1</sup>Central Michigan Univ., Mt Pleasant, MI; <sup>2</sup>Col. of Med., Central Michigan Univ., Mount Pleasant, MI; <sup>3</sup>Psychology/Program in Neurosci., CENTRAL MICHIGAN UNIVERSITY, MOUNT PLEASANT, MI

**Abstract:** Despite growing knowledge of spinal cord injury (SCI) pathophysiology, treatments for the permanent functional deficits resulting from SCI remain scarce. Methylprednisolone (MP), despite demonstrating mixed clinical efficacy in the management of acute SCI, has shown promise in reducing neuroinflammation and promoting functional recovery in recent animal studies. Etanercept (ETN), a tumor necrosis factor (TNF) inhibitor, has recently gained special attention in SCI discourse due to its potential neuroprotective effects following SCI. To evaluate the effects of MP and ETN, both as monotherapies and in combination, administered systemically or intrathecally following SCI. Forty-eight Wistar rats underwent T9 clip-compression SCI and randomized to one of eight treatment groups (n = 6 / group) of either systemic saline, systemic MP, systemic ETN, systemic MP + ETN, intrathecal saline, intrathecal

MP, intrathecal ETN, or intrathecal MP + ETN. Treatments were administered 30 minutes after SCI. Locomotor function was evaluated pre-injury, 3-days post-injury, and weekly thereafter for six weeks using the Basso, Beattie, Bresnahan locomotor rating scale (BBB). Blinded researchers scored each video-recorded session using the standardized BBB scale, with higher BBB scores indicating greater motor function. On interim analysis, repeated-measures ANOVA of BBB scores revealed a significant interaction between injection type and treatment allocation over time. Thus far, intrathecal MP seemed to significantly reduce average BBB scores as compared to intrathecal saline, whereas intrathecal ETN demonstrated noninferiority to intrathecal saline. Rats receiving intrathecal ETN seemed to demonstrate significantly greater BBB scores than rats receiving intrathecal MP. This study is the first to compare systemic and intrathecal ETN, MP, and their combination in a rat SCI model. Preliminary findings suggest that intrathecal MP may hinder the functional recovery of rats following SCI. Evaluation of the treatments' effects on white and grey matter sparing, systemic and local TNF levels, and splenic CD68 levels are ongoing and will provide a more comprehensive assessment.

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## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.16/J5

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** CONACYT

**Title:** Estudio isobolográfico para determinar la dosis-respuesta de la combinación de dapsona y N-acetilcisteína en un modelo de rata con lesión medular traumática.

**Authors:** \*H. ROMERO SÁNCHEZ<sup>1</sup>, C. RIOS<sup>2</sup>, A. MATA-BERMUDEZ<sup>3</sup>, A. DIAZ-RUIZ<sup>4</sup>;

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**Abstract: Title:** *Isobolographic analysis of the antinociceptive and antioxidant interaction between dapsona and N-acetylcysteine in a rat model of spinal cord injury* **Abstract:**

Neuropathic pain resulting from spinal cord injury (SCI) is a complex and multifactorial condition with limited effective treatments. In this study, we investigated the potential synergistic interaction between dapsona (DDS) and N-acetylcysteine (NAC) in reducing hyperalgesia and oxidative stress following SCI in rats. Adult male Wistar rats were subjected to traumatic SCI, and treatment groups received DDS, NAC, or their fixed-ratio combinations intraperitoneally. Behavioral assessments were performed using the Von Frey filament test for

mechanical hyperalgesia and the hot plate test for thermal sensitivity. To evaluate oxidative stress, we measured malondialdehyde (MDA) and reduced glutathione (GSH) levels in spinal cord tissue. Dose-response curves were established for each compound, and isobolographic analysis was used to determine the type of pharmacological interaction. Additionally, molecular docking was employed to explore potential binding affinities and complementary mechanisms of action at inflammatory and oxidative molecular targets. Results indicate that the DDS-NAC combination significantly enhanced antinociceptive responses and improved redox status, showing a clear synergistic interaction in both behavioral and biochemical parameters. This supports the hypothesis that combining an anti-inflammatory sulfone drug with a thiol-based antioxidant may produce multimodal benefits in the management of SCI-induced neuropathic pain. These findings suggest that DDS and NAC could represent a promising therapeutic strategy for developing safer and more effective treatments targeting both nociceptive and oxidative components of neuropathic pain after spinal trauma.

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## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.17/J6

**Topic:** D.05. Spinal Cord Injury and Plasticity

**Support:** Department of the Army – USAMRAA HT9425-23-1-0562 (SC220248).  
We thank Dr. Evan Unger, Executive Chairman and Co-Founder of  
NuVox Therapeutics, for providing NanO<sub>2</sub>.

**Title:** Intravenous NanO<sub>2</sub> Therapy Attenuates Secondary Injury and Enhances Functional Recovery Following Cervical Spinal Cord Contusion in Rats

**Authors:** \*J. HOU<sup>1,2</sup>, C. DOWNIE<sup>2,1</sup>, C. BROWN<sup>2,1</sup>, D. PLANT<sup>1</sup>, A. PULLOS<sup>1</sup>, K. S. KLIPPEL<sup>2,1</sup>, F. CHEUNG<sup>1</sup>, G. HWANG<sup>2,1</sup>, S. TSUDA<sup>2,1</sup>, G. CHENG<sup>1</sup>, G. A. VARGAS<sup>2,1</sup>, C. GARVAN<sup>2</sup>, B. SPIESS<sup>2</sup>, F. J. THOMPSON<sup>1,3</sup>, P. K. BOSE<sup>1,2,4</sup>;  
<sup>1</sup>North Florida/South Georgia Veterans Hlth. Syst., Gainesville, FL; <sup>2</sup>Anesthesiol., <sup>3</sup>Neurosci., <sup>4</sup>Neurol., Univ. of Florida Col. of Med., Gainesville, FL

**Abstract:** Cervical spinal cord injury (C-SCI) frequently results in lasting locomotor deficits, significantly impairing independence and quality of life. While the primary mechanical trauma initiates immediate damage, progressive secondary injury processes—characterized by ischemia, oxidative stress, and inflammation—amplify tissue loss and worsen neurological outcomes. Therefore, therapies that target these secondary cascades hold promise for improving recovery. We investigated the neuroprotective potential of NanO<sub>2</sub>, an intravenous emulsion of perfluorocarbon (PFC) nanoparticles (NuVox, Therapeutics, Tucson, AZ), designed to enhance

oxygen delivery and limit ischemia-induced damage. Adult female Sprague-Dawley rats underwent moderate C6/7 spinal cord contusions (200 kdynes, Infinite Horizon Impactor) under anesthesia. Animals were randomized to receive either NanO<sub>2</sub> (0.6 ml/kg; initial dose at 20 minutes post-injury, followed by two additional doses at 90-minute intervals) or normal saline (NS), administered via lateral tail vein using a WPI syringe pump at 50 µl/min. Functional assessments included 3D kinematic gait analysis (SIMI Motion Systems) and CatWalk XT (Noldus) automated footprint tracking at pre- and post-injury timepoints. Hindlimb spasticity was evaluated at post-operative weeks 4 and 8 using velocity-dependent ankle torque measurements, time-locked triceps surae EMG responses, and H-reflex rate-depression testing. In vivo 7T (MR Solution) fast spin echo (FSE) MRI was conducted at weeks 1, 4, and 8 to quantify lesion volume, edema, and anatomical characteristics of the injury site. Immunohistochemical analyses were performed on spinal cord tissue to assess expression of inflammatory and oxidative stress markers, including IL-1 $\beta$ , NF $\kappa$ B, and Nitrotyrosine (3-NT). Results to date demonstrate that NanO<sub>2</sub>-treated animals exhibited significantly improved locomotor function and reduced hindlimb spasticity compared to controls. MRI revealed smaller lesion volumes, and histological data showed decreased expression of pro-inflammatory and oxidative stress markers in NanO<sub>2</sub>-treated tissue. These findings suggest that NanO<sub>2</sub> effectively mitigates ischemia-driven secondary injury mechanisms and improves functional outcomes following C-SCI. This therapy represents a promising candidate for future translation in acute spinal cord injury management.

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## **Poster**

### **PSTR218: Spinal Cord Injury: Therapeutic Strategies: *In Vivo*: Pharmacological**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR218.18/J7

**Topic:** D.05. Spinal Cord Injury and Plasticity

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Merit Review Award # B3986-R/1 I01 RX003986-01A1, from the United States Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D).

**Title:** Neurobiological Insights into Spinal Cord Injury and Motor Recovery with Iron Chelator Therapy in a Rodent Model



**Authors:** \***P. K. BOSE**<sup>1,2,3</sup>, J. HOU<sup>1,2</sup>, S. TSUDA<sup>2,1</sup>, D. PLANT<sup>1</sup>, G. CHENG<sup>1</sup>, G. A. VARGAS<sup>2,1</sup>, C. BROWN<sup>2,1</sup>, C. DOWNIE<sup>2,1</sup>, A. PULLOS<sup>1</sup>, K. S. KLIPPEL<sup>2,1</sup>, N. M. WESTON<sup>1</sup>, G. HWANG<sup>2,1</sup>, A. KUMAR<sup>5</sup>, R. BERGERON<sup>6</sup>, F. J. THOMPSON<sup>1,4</sup>;  
<sup>1</sup>North Florida/South Georgia Veterans Hlth. Syst., Gainesville, FL; <sup>2</sup>Anesthesiol., <sup>3</sup>Neurol., <sup>4</sup>Neurosci., Univ. of Florida Col. of Med., Gainesville, FL; <sup>5</sup>Dept Neuroscience, McKnight Brain Inst., Univ. of Florida, Gainesville, FL; <sup>6</sup>Medicinal Chem., Univ. of Florida Col. of Pharm., Gainesville, FL

**Abstract:** Cervical spinal cord injury (C-SCI), commonly caused by trauma, is a major contributor to long-term disability, resulting in chronic impairments such as spasticity, gait dysfunction, and loss of independence. One key driver of secondary injury after contusive SCI is hemorrhagic “free iron,” which accumulates at the injury site, disrupts the blood-spinal cord barrier (BSCB), and catalyzes the production of reactive oxygen species (ROS). This cascade exacerbates oxidative stress and neuroinflammation, contributing to irreversible neurodegeneration. Despite these well-established pathological mechanisms, no approved therapies effectively target hemorrhagic iron or its downstream effects. This study evaluates the safety and therapeutic efficacy of SP420, a novel, systemically administered iron chelator, using a validated rodent model of moderate C-SCI. We hypothesized that SP420, delivered after injury, would eliminate hemorrhagic iron toxicity, attenuate secondary damage, and improve functional recovery. Injuries were induced at C6/7 via a 200-kdyne impact under anesthesia and aseptic conditions. SP420 was administered subcutaneously under various acute and chronic dosing paradigms to test therapeutic timing and durability. Acute dosing included 66 mg/kg every other day for 2 weeks, beginning either 30 minutes post-injury or at post-injury week 1. Chronic dosing involved 80 mg/kg, delivered either from post-injury week 4 for 2 or 3 weeks, or from week 12 for 3 weeks. Control animals received saline. Group sizes and bias were minimized through blinding, randomization, and protocol standardization. Primary outcomes included assessments of spasticity, axonal conduction via motor evoked potentials, 3D kinematic gait analysis, and digital footprint evaluation. Structural and functional changes were assessed using multimodal MRI (T1/T2-weighted, SWI, QSM, and DTI). Safety was monitored via clinical health indicators and liver, kidney, and hemoglobin panels. Histological and immunohistochemical analyses quantified iron burden, oxidative stress, neuroinflammation, BSCB integrity, and neurovascular preservation. SP420 significantly reduced oxidative damage and inflammation, preserved descending motor tracts, promoted neuroplasticity, and improved motor function. Ex vivo DTI confirmed enhanced corticospinal and rubrospinal tract integrity. SP420 was well tolerated, with no evidence of systemic toxicity. These results support SP420 as a promising, non-invasive therapeutic for SCI and provide preclinical data suitable for an FDA investigational new drug (IND) application.

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**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.01/J8

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH NEI U01 EY034680-03

**Title:** Changes in Melanopsin Expression in the Iris and Retina After Corneal Abrasion

**Authors:** \*A. JENIKE<sup>1</sup>, S. ZEIMANTZ<sup>2</sup>, D. M. HEGARTY<sup>2</sup>, T. HILTON<sup>2</sup>, T. M. LARGENT-MILNES<sup>4</sup>, C. W. MORGANS<sup>3</sup>, S. A. AICHER<sup>2</sup>;

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**Abstract:** This study examined the changes in expression of melanopsin in the pupillary margin of the iris and retina of male and female rats after a unilateral corneal abrasion. Melanopsin is involved in not only the pupillary light reflex but also vascular development and melanogenesis. Iridial melanopsin expression outside of the pupillary constrictor muscle may have a dynamic response to injury in the surrounding ocular tissues. In the present study, unilateral corneal abrasions were performed on male and female Sprague-Dawley rats and ocular tissues were collected at two post-abrasion time points. Ocular pain was quantified by scoring orbital tightening (OT) before abrasion (baseline), 24 hrs and one-week post-abrasion as well as in control rats. In the iris, immunohistochemistry was used to label melanopsin, smooth muscle alpha-actin, and beta-tubulin. Four regions of the iridial pupillary margin were then imaged on a Zeiss LSM 900 confocal microscope with a 40x oil immersion objective. Melanopsin in the stroma and epithelial layers of the pupillary margin was measured as a volume using Imaris software. The retina was labeled for melanopsin and imaged on an Apotome microscope at 10x. The number of melanopsin positive retinal ganglion cells (RGS) was counted using Arrivis software. The volume of melanopsin, which was normalized to  $5.0 \times 10^5 \mu\text{m}^3$  and reported as mean  $\pm$  SEM, was then compared between abraded and control animals, within each sex at each time point. The average volume of melanopsin in the stroma and epithelial layers was higher 24 hrs after abrasion (Males:  $2920.9 \pm 584.4 \mu\text{m}^3$ , N=3, 2-way ANOVA P=0.006; Female:  $2997.6 \pm 547.3 \mu\text{m}^3$ , N=3, 2-way ANOVA, P=0.001) compared to control irises (Male:  $1164.7 \pm 229.1 \mu\text{m}^3$ , N=3; Female:  $772.4 \pm 185.8 \mu\text{m}^3$ , N=3). After one week, the volume of melanopsin outside of the constrictor muscle in the iris returned to control levels. Within control animals, we found a sex difference with male rats having a higher melanopsin volume than female rats (t-test, P=0.016). The melanopsin positive RGC in the retina were also counted. Control male retinas had more melanopsin positive cells ( $1231.12 \pm 35.85 \text{ cells}/25\text{mm}^2$ , N=3) than control female retinas ( $910.79 \pm 81.32 \text{ cells}/25\text{mm}^2$ ; 2-way ANOVA, N=3, P=0.011). The number of melanopsin positive cells in males ( $899.28 \pm 80.81 \text{ cells}/25\text{mm}^2$ , N=3) decreased 24 hrs after abrasion (2-way ANOVA, P=0.008) while it remained the same in females. Taken together this study shows that melanopsin is expressed differently in males and females. These data also show that in the iris there is a dynamic response in melanopsin after corneal abrasion and possibly a sex-specific response in the retina.

**Disclosures:** A. Jenike: None. S. Zeimantz: None. D.M. Hegarty: None. T. Hilton: None. S.A. Aicher: None.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.02/J9

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NEI Grant REY026147D

**Title:** Structural characterization of N- and O-glycans of the trigeminal ganglia of male and female mice

**Authors:** \*K. A. RYBKA, P. ARGUESO;  
Ophthalmology, Tufts Med. Ctr., Boston, MA

**Abstract:** The cornea is the most densely innervated and sensitive tissue in the body, with approximately 7,000 nerve terminals per square millimeter. These sensory nerves have cell bodies that predominantly originate from the ophthalmic branch of the trigeminal ganglion. The trigeminal ganglion is a critical peripheral nervous system structure responsible for detecting physical and chemical stimuli at the ocular surface and transmitting sensory information to the brain. Glycans-complex carbohydrate structures classified into several categories including N- and O-glycans-play key roles in cellular communication, protein function, neural activity, and sensory perception. This study aims to comprehensively characterize the N- and O-glycan structures present in the trigeminal ganglion to better understand how glycosylation may modulate corneal innervation and sensory function. Trigeminal ganglia were collected from 6-8-week-old male and female C57BL/6J wild-type mice. Trigeminal ganglia from 5 mice were pooled per sample and analyzed in biological triplicates. Samples were frozen at -80°C for 24h before undergoing lyses, homogenization and glycan extraction using porous graphitized carbon-liquid chromatography-mass spectrometry (PGC-LC-MS/MS). N-glycans were released enzymatically with PNGase F, while O-glycans were released via  $\beta$ -elimination. Data analysis was performed using GraphPad Prism, Thermo Freestyle, and Skyline software. Mass spectrometry identified 58 unique N-glycans and 16 unique O-glycans in the mouse trigeminal ganglion. The N-glycan profile was characterized primarily by high-mannose and biantennary complex structures, with core-fucosylation serving as the most prevalent modification and accounting for approximately 36% of the total. The most abundant N-glycan was a core-fucosylated, unsialylated bisecting structure, which was found at significantly higher levels in males compared to females. O-glycans were predominantly sialylated, comprising 82% of the total O-glycan profile, with a bi-sialylated core 1 structure being the most prominent. Our findings provide valuable information on the glycomic profile of the mouse trigeminal ganglion, revealing a glycan composition dominated by fucosylated N-glycans and sialylated O-glycans. The overall glycan profile closely resembles that of the brain, with minimal sex differences observed.

**Disclosures:** K.A. Rybka: None. P. Argueso: None.

## Poster

### PSTR219: Headache, Migraine, and Trigeminal Circuits

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.03/J10

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH/NEI Grant U01EY034709  
NIH/NIGMS Grant P30GM145497

**Title:** Comprehensive labeling of corneal afferent neurons in mice using intrastromal AAV delivery and Cre-reporter lines

**Authors:** \*S. REYNOLDS<sup>1,2</sup>, K. NIYONKURU<sup>2</sup>, B. MERRILL<sup>1</sup>, W. RENTHAL<sup>3</sup>, I. D. MENG<sup>2</sup>;

<sup>1</sup>Grad. Sch. of Biomed. Sci. and Engin., Univ. of Maine, Orono, ME; <sup>2</sup>Univ. of New England, Biddeford, ME; <sup>3</sup>Neurol., Brigham and Women's Hosp., Boston, MA

**Abstract:** The cornea is highly innervated by A-delta and C-fibers that convey sensory information to the CNS; yet a comprehensive characterization of these neurons, and a detailed map of their projections, has not been described in the mouse. In this study we utilized AAV delivery to the mouse cornea, testing multiple combinations of AAV serotype, promoters, and Cre-reporter mice, to determine the optimal approach to labeling corneal projecting afferents. Intrastromal injections of AAV were performed in 5-8 wk old mice. AAV expression of tdTomato in C57BL/6 mice and Cre in Ai14 (tdTomato) and CAG-Sun1/sfGFP reporter mice was used to visualize corneal projecting neurons; viruses utilizing both hSyn and CAG promoters were also tested. Mice were perfused 2-5 weeks after injections; corneas, trigeminal ganglia (TG), and brains were extracted. Corneas were examined for tdTomato-positive corneal nerve innervation. Cell bodies of corneal projecting neurons were quantified in whole, tissue-cleared TG. Thick sections (300 µm) of brain through the second cervical vertebra were cleared and confocal images were used for identifying central projections. An initial comparison of AAV9, AAV-PHP.S, and AAV2-Retro serotypes indicated greater transduction efficiency for AAV2-Retro and AAV9. Expression of Cre in reporter mice had greater sensitivity in labeling corneal projecting neurons compared to direct AAV expression of tdTomato or WGA injection in B6 mice. Intrastromal injections of AAV labeled peripheral nerves innervating the cornea, with tdTomato-positive fibers present in the stromal bundles, subbasal nerve plexus, and free nerve endings. Labeled cell bodies in the TG were located almost exclusively on the medial portion of the first branch and consistently distributed across all labeling approaches. Dense central projections were identified in two distinct regions of the spinal trigeminal nucleus (Vsp), one located in the ventral portion of the anterior spinal trigeminal subnucleus caudalis (Vc) and the other located in more posterior Vc. Additional moderate projections to the trigeminal nucleus principalis and sparse projections to the parabrachial nucleus were also present. AAV2-Retro transduction following corneal intrastromal injections provides robust labeling of corneal primary afferent neurons, allowing for the identification of central projection targets. Successful

nuclear-envelope labeling in CAG-Sun1/sfGFP reporter mice provides a promising method for labeling corneal afferents for snRNA-seq and spatial transcriptomics.

**Disclosures:** S. Reynolds: None. K. Niyonkuru: None. B. Merrill: None. W. Renthal: None. I.D. Meng: None.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.04/J11

**Topic:** E.06. Vision

**Support:** NEI U01EY034687  
NIH P30 EY07551

**Title:** Targeting Corneal Sensory Neurons For Molecular Profiling

**Authors:** \*W. PEREZ<sup>1</sup>, M. RASHEED<sup>1</sup>, S. PARIKH<sup>2</sup>, S. MITRA<sup>1</sup>, A. MATYNIA<sup>3</sup>;  
<sup>1</sup>Univ. of Houston, Houston, TX; <sup>2</sup>UCLA, Los Angeles, CA; <sup>3</sup>Col. of Optometry, UCLA, Houston, TX

**Abstract: Purpose:** The cornea is the most innervated tissue in the body, yet only 1% are known to be corneal projecting trigeminal ganglion neurons (cpTGs). These rare neurons play essential roles in pain sensation, blink reflex, and tear production. A major limitation in studying cpTGs has been the inability to reliably and selectively label them. Here, we present minimally invasive methods to specifically label cpTGs. Using this approach, we identify A $\delta$  fiber neurons, C-fibers neurons, and Piezo2-positive neurons within the cpTGs population. This method provides a foundation for studying cpTGs corneal sensory function. **Methods:** AAV serotypes 1, 2, 6, 8 and 9 with a reporter gene, and the classic retrograde tracers FM1-43 and FM4-64 were evaluated using corneal intrastromal injections for spatial selectivity in wild type mice. Controls included intraperitoneal (IP) injections of the tracers or mice with a genetic ablation of nociceptors (Nav1.8-Cre;Rosa-DTA). Corneas and trigeminal ganglia were assessed via immunofluorescence microscopy (FV3000 or Leica Thunder) for reporter expression. Morphometric analysis was used to classify cpTGs as A $\delta$  or C-fiber neurons. Piezo2-positive neurons were identified by uptake of FM1-43 or FM4-64. **Results:** Viral reporter gene expression was detectable in cpTGs somata as early as 2 weeks post-injection, with expression levels increasing through 8 weeks in both A $\delta$  or C-fiber neurons. Expression in corneal nerve fibers was positively correlated to the number of labeled cpTGs somata. The efficiency of cpTGs labeling per trigeminal ganglia using intrastromal injections at 1-week post-injection was 117 for AAV6 (n=2), 74 for AAV8 (n=2), 59 for AAV9 (n=2), and 5 for AAV2 (n=2). By 2-4 weeks post-injection, we observed 218 cpTGs for AAV6 (n=3) and 89 for AAV1 (n=12). By contrast, wild type mice with intrastromal injections of FM1-43 (n=12) or FM4-64 (n= 10) and mice lacking Nav1.8-expressing nociceptors injected with AAV6 (n=6) had 0 cpTGs per trigeminal

ganglia. Control IP injections of FM1-43 and FM4-64 labeled many TG neurons. **Conclusions:** AAV6 exhibits strong tropism for cpTGs compared to other AAV serotypes or retrograde tracers when delivered by intrastromal injection. AAV intrastromal injection in conjunction with Piezo2-specific retrograde tracers would facilitate a deeper exploration of cpTGs. This strong targeted tropism of AAV6 for cpTGs offers the potential to specifically alter corneal nerve function through gene therapy.

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## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.05/J12

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH grant PAF06292

**Title:** Comprehensive Transcriptomic and anatomical cell type classification of Mouse Brainstem Trigeminal Nuclei

**Authors:** \*J.-C. HSIEH<sup>1</sup>, X. NIU<sup>3</sup>, M.-C. CHENG<sup>2</sup>, D. CAI<sup>4</sup>;

<sup>1</sup>Michigan Neurosci. institute, <sup>2</sup>Univ. of Michigan, Ann Arbor, MI; <sup>3</sup>UNIVERSITY OF MICHIGAN, Ann Arbor, MI; <sup>4</sup>Cell and Developmental Biol., Michigan Neurosci. Institute, Univ. of Michigan, Ann Arbor, MI

**Abstract:** The brainstem trigeminal nuclei (TGN) serve as crucial sensory relays, processing inputs from the trigeminal ganglia and transmitting them to higher brain centers, such as the thalamus and primary/secondary somatosensory regions. Due to limited data on transcriptome and morphology, neurons subtypes residing in the TGN are not well classified. To fill this gap, we aim to comprehensively map the transcriptomic profiles and reconstruct neuron morphology of the mouse TGN. We first performed single-nucleus RNA sequencing and revealed 35 distinct cell clusters in the lateral brainstem, with 17 clusters associated with known regions of the brainstem trigeminal nuclei (PsV, SpVI, SpVO, SpVC). Significant marker genes were identified and validated by multiplex in-situ mRNA profiling, enhancing our understanding of the specific molecular profiles within these clusters. To establish a molecular connectome atlas of the mouse TGN, we developed a novel protocol to enable multi-plex in-situ mRNA-and-protein co-profiling. Neuron morphology, synaptic contacts, and mRNA markers are profiled within large, expanded sample volumes, which resulted in the classification of molecular-and-structural classification of TGN neuron subtypes. Our finding provides critical insights into the neuron cell types and organization of the trigeminal sensory system and lays the groundwork for further exploration of its role in sensory gating and associated behaviors.

**Disclosures:** J. Hsieh: None. X. Niu: None. M. Cheng: None. D. Cai: None.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.06/J13

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Molecular Characterization of the Nitroglycerin Model in Rodents Using Single Nucleus RNA-Sequencing

**Authors:** \*U. PFISTERER<sup>1</sup>, V. A. CARMELO<sup>1</sup>, J. ROMERO HERRERA<sup>1</sup>, C. HUNDAHL<sup>1</sup>, C. LAURITZEN<sup>2</sup>, F. WICHERN<sup>3</sup>, T. BENNED-JENSEN<sup>1</sup>;

<sup>1</sup>Mol. and Single Cell Pharmacol., <sup>2</sup>Dept. of Symptom Biol., <sup>3</sup>Dept. of Histology and Pathology Models, H. Lundbeck A/S, Copenhagen, Denmark

**Abstract:** Migraine-like behavior and neuropathic pain are commonly studied using the nitroglycerin (NTG) model in rodents, which exists in both acute and chronic forms. This study aims to elucidate the molecular mechanisms underlying these conditions through single-nucleus RNA sequencing (snRNA-seq). Behavioral assessment in form of the von Frey test was employed to select animals for analysis based on their mechanical nociception responses consequently to single (acute) or five consecutive (chronic) NTG injections. snRNA-seq was conducted on four key regions implicated in neuropathic pain: the trigeminal ganglion (TG), meninges (M), spinal trigeminal nucleus (SP5C), and sphenopalatine ganglion (SPG). While SPG analysis was carried in the chronic NTG model exclusively pooling eight animals per condition, the TG, M and SP5C were processed per individual animal (n=3) per condition (acute, chronic and corresponding Veh-injected animals). This led to the generation of a cell atlas of the acute and chronic NTG model comprising >430 000 nuclei passing quality filtering. Following cell type annotations per region downstream analysis revealed both global and localized gene expression differences, highlighting disease model-related transcriptional changes. Molecular distances were mapped, identifying specific cell types most affected by the NTG model manifested in distinct cell type per region. This study provides a comprehensive molecular profile of the NTG model, offering valuable insights into one of the most frequently used preclinical models of migraine-like and neuropathic pain.

**Disclosures:** U. Pfisterer: None. V.A. Carmelo: None. J. Romero Herrera: None. C. Hundahl: None. C. Lauritzen: None. F. Wichern: None. T. Benned-Jensen: None.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.07/J14

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** Howard Hughes Medical Institute Hanna H. Gray Fellowship  
NIH RF PA20-18

**Title:** Longitudinal trigeminal ganglion sensory encoding in anesthetized and awake mice

**Authors:** \*B. O. AHANONU<sup>1</sup>, D. MOHSENIN<sup>2</sup>, X. YU<sup>3</sup>, A. I. BASBAUM<sup>4</sup>;

<sup>1</sup>Univ. of California, San Francisco, San Francisco, CA; <sup>2</sup>Univ. of California: San Francisco, San Francisco, CA; <sup>3</sup>Anesthesiol., Univ. of California San Francisco, San Francisco, CA; <sup>4</sup>Dept of Anat., UCSF, San Francisco, CA

**Abstract:** Background & Aims

The face is a key area for sensory processing across the animal kingdom. Facial somatosensory information is processed by trigeminal ganglion neurons (TGNs), which transmit information to the nucleus caudalis and then to the brain. This processing can become aberrant, as is hypothesized to occur in trigeminal neuralgia (TN), a devastating pain condition with significant need for treatment beyond carbamazepine. Understanding how TGN computation relates to perception and behavior and how this changes in chronic pain and analgesic states necessitates recording TGN activity over time and in behaving animals. To address these gaps, here we longitudinally imaged TGN activity in anesthetized and awake animals.

Methods

We developed and validated a calcium imaging approach to record from TGNs over time. We expressed jRCaMP1a in sensory neurons and implanted a microendoscopic (GRN) lens over the trigeminal ganglion. We imaged TGNs using head-fixed one-photon or freely moving miniature microscopy and delivered stimuli to the face while monitoring face temperature. For awake mice, we concurrently monitored and quantified behavior.

Results

We monitored animals for weeks to over a month after surgery and found that behavior recovered. In vivo microCT imaging validated GRN lens placement. We observed TGNs stimulus-evoked activity to ipsilateral—but not contralateral—thermal, mechanical (including whisker manipulation), and pruritogenic stimuli, in anesthetized and in awake, behaving animals. We recorded stimulus-responsive TGNs, often daily, and in others for weeks to over a month. Tracking TGNs across sessions with CIAtah ([git.io/ciatah](https://git.io/ciatah)) revealed a subset of TGNs that maintained their coding properties for days. Facial nerve block eliminated TGN stimulus-evoked activity; critically, the next day, stimulus evoked activity was restored. In awake animals, some stimulus-evoked activity was recorded in TGNs with or without post-stimulus behavior.

Conclusions

Longitudinal TGN imaging reveals that TGNs can stably encode sensory information and this is not altered by transient pharmacological intervention. With this approach we are now able to monitor individual TGNs in response to injury (e.g. trigeminal pain models) and analgesics (e.g. carbamazepine) while relating TGN activity to behavioral outcomes, allowing for a neurobehavioral approach to screening novel therapies for facial pain. Critically, the finding that



TGN stimulus-evoked activity does not always correlate with behavioral responses emphasizes the need to investigate the relationship between peripheral and central nervous system activity in awake animals.

**Disclosures:** **B.O. Ahanonu:** None. **D. Mohsenin:** None. **X. Yu:** None. **A.I. Basbaum:** None.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.08/Web Only

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** IN202222 (MCL)  
IN218122 (AGH)  
MCL (grant DGAPA-UNAM)

**Title:** Bifurcated projections from the trigeminal ganglion cells to the infraorbital nerve and transverse sinus: correlation with the oxytocin receptor and CGRP.

**Authors:** \***G. MARTINEZ-LORENZANA**<sup>1</sup>, **A. CÓRDOVA QUIROGA**<sup>2</sup>, **A. GONZÁLEZ-HERNÁNDEZ**<sup>3</sup>, **M. CONDES-LARA**<sup>4</sup>;

<sup>1</sup>Inst. de Neurobiología, UNAM., Querétaro, Mexico; <sup>3</sup>Inst. de Neurobiología, <sup>2</sup>Inst. de Neurobiología, UNAM, Queretaro, Mexico; <sup>4</sup>Univ. Nacional Autonoma De Mexico, Queretaro, Mexico

**Abstract:** The first branch of the trigeminal nerve (V1, ophthalmic) is linked to the pathophysiology of migraine headaches. A key model suggests that a single wide dynamic range (WDR) cell in the trigeminocervical complex receives input from the V1 branch, which innervates the periorbital and meningeal regions. Limited evidence also indicates a role for the V2 branch (maxillary). To explore this, we conducted experiments using retrograde neural tracers in adult (60 days postpartum) and young (30 days postpartum) male Wistar rats to investigate neuronal convergence in the trigeminal ganglion (TG) from both branches. True-Blue (TB) was injected at the V1 level, and Fluoro-Gold (FG) at the V2 level. We analyzed the relationship between the oxytocin receptor (OTR), calcitonin gene-related peptide (CGRP), and isolectin B4 (IB4) in the TG and meningeal structures. Several TG cells were labeled with FG and TB, indicating convergence from both branches. Young animals had more labeled cells than adults, suggesting developmental changes in craniofacial innervation. At the meningeal level, OTR was expressed around blood vessels and with CGRPergic fibers. These findings suggest that individual TG cells can project through both the V1 and V2 branches, with OTR present in meningeal structures related to headache nociception. This supports earlier studies highlighting OTR's role in inhibiting CGRPergic nerve activity.

**Disclosures:** **G. Martinez-Lorenzana:** None. **A. Córdova Quiroga:** None. **A. González-Hernández:** None. **M. Condes-lara:** None.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.09/J15

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** TTUHSC startup funds (JLW)

**Title:** Age and sex influence migraine-like phenotypes in a mouse model of chronic migraine

**Authors:** \*K. FRIMPONG-MANSON, J. WILKERSON;  
Dept. of Pharmaceut. Sci., TTUHSC, Amarillo, TX

**Abstract:** Chronic migraine disproportionately affects females, and while immune changes may affect its pathophysiology, it is unclear if these changes are sex-specific. Additionally, the prevalence of migraine has been shown to peak around middle age, yet age is an understudied biological factor in preclinical migraine research, which limits translational validity. To explore sex- and age-related differences in migraine-like phenotypes, we treated 88 male and female young (8 to 10 weeks), and middle-aged (40 to 42 weeks) C57BL/6J mice, with intraperitoneal injections of either nitroglycerin (10 mg/kg) or saline. In one group, treatments were administered on five alternating days (9 days), and a blinded experimenter conducted von Frey assay to assess extracephalic (hind paw) mechanical allodynia. Another group of sex- and age-matched mice underwent a similar testing paradigm for 5 days and were euthanized at the end of the study. Their plasma and cortex were collected because these are primary sites of systemic and neurogenic migraine-associated immune processes. The samples were analyzed with the Luminex multiplex assay to quantify the concentration of soluble immune proteins, which have important but poorly defined roles in migraine pathology. Specifically, we were interested in the following proteins: interleukin-1-beta (IL-1 $\beta$ ), interferon-gamma (IFN- $\gamma$ ), interleukin-15 (IL-15), and interleukin-2 (IL-2). We observed robust nitroglycerin-induced mechanical allodynia in both sexes of young mice, but not in middle-aged mice. Young female mice treated with nitroglycerin had significantly elevated plasma levels of IL-1 $\beta$ , with significant decreases in IFN- $\gamma$  and IL-15. Additionally, IL-2 was significantly decreased in the cortex of these female mice. There was no significant difference in protein expression between nitroglycerin and saline-treated young male mice or both sexes of middle-aged mice. Collectively, the data suggest that immune-related mechanisms may play a predominant role in migraine pathology in females than in males. While we did not observe nitroglycerin-evoked pain in middle-aged mice and corresponding immune changes, this novel finding highlights the need to consider age as an important biological factor in preclinical chronic migraine studies.

**Disclosures:** K. Frimpong-Manson: None. J. Wilkerson: None.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.10/J16

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH contract 75N95024D00038

**Title:** Characterization of the isosorbide dinitrate model of headache in male and female rats

**Authors:** Y. ZHANG<sup>1</sup>, M. CIKLIC<sup>2</sup>, **M. URBAN**<sup>4</sup>, E. DUGAN<sup>4</sup>, C. CONRAD<sup>5</sup>, V. BRINGS<sup>6</sup>, S. A. WOLLER<sup>7</sup>, S. IYENGAR<sup>8</sup>, T. HANANIA<sup>4</sup>, \*M. A. VARNEY<sup>3</sup>;

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**Abstract:** Rat models of headache have been described in which facial mechanical allodynia is produced following systemic administration of nitric oxide donor compounds. In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we characterized the behavioral pain phenotype and pharmacology associated with a rat model of headache involving single or repeated administration of the nitric oxide donor isosorbide dinitrate (ISDN). Adult male and female Sprague Dawley rats were used in these studies, and effects of ISDN (10 mg/kg, IP) were examined following single and repeated administration. Facial mechanical allodynia was measured by applying calibrated von Frey filaments to the periorbital region of the face and determining mechanical sensitivity thresholds. Study groups were randomized, the investigators were blinded to treatment, and groups were sufficiently powered to identify statistically significant effects. A single administration of ISDN produced facial mechanical allodynia in male and female rats which was observed for a period of 4 hours. Repeated administration of ISDN once per day for four consecutive days produced persistent facial mechanical allodynia which was observed for at least 24 hours following the final administration. Pretreatment with the mu opioid receptor agonist morphine sulfate (0.3, 1, 3, and 6 mg/kg, SC), 5-HT<sub>1B/1D</sub> agonist sumatriptan (0.1, 0.3 and 1 mg/kg, IP), CGRP receptor antagonist olcegepant (0.3, 1, and 3 mg/kg, IP), and delta opioid receptor agonist SNC80 (3, 10, and 30 mg/kg, SC) suppressed the development of ISDN-induced facial allodynia in a dose-dependent manner. We are continuing to evaluate the effects of reference analgesics on transient and persistent facial mechanical allodynia following single and repeated administration of ISDN, respectively. Additionally, we are planning to evaluate non-evoked behavioral pain endpoints (i.e. orbital tightening) and altered sensitivity associated with migraine (i.e. photophobia/phonophobia) to further characterize this model. The data to date support the use of this model to identify potential treatments for headache disorders as part of the NIH HEAL initiative to identify novel, non-opioid treatments for pain.

**Disclosures:** **Y. Zhang:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **M. Ciklic:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **M. Urban:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **E. Dugan:** A. Employment/Salary

(full or part-time): PsychoGenics Inc. **C. Conrad:** A. Employment/Salary (full or part-time): NIH/NINDS. **V. Brings:** A. Employment/Salary (full or part-time): NIH/NINDS. **S.A. Woller:** A. Employment/Salary (full or part-time): NIH/NINDS. **S. Iyengar:** A. Employment/Salary (full or part-time): NIH/NINDS. **T. Hanania:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **M.A. Varney:** A. Employment/Salary (full or part-time): PsychoGenics Inc.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.11/K1

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Comparative evaluation of KCl-induced and Nitroglycerin-induced migraine models in rats

**Authors:** \*E. ESNEAULT, G. PEYON, E. SABLÉ, E. CAMPEROS, C. RONDEAU, S. PEDRON;  
Porsolt, Le Genest St Isle, France

**Abstract:** Animal models are critical tools for investigating migraine pathophysiology and evaluating the efficacy of novel therapeutic candidates. Model selection is typically based on their mechanistic alignment with distinct migraine subtypes. Migraine with aura, which affects approximately 25-30% of migraine patients, can be modelled using potassium chloride (KCl), which induces cortical spreading depression, while migraine without aura, representing the remaining 70-75% of cases, can be mimicked by administering a nitric oxide donor such as nitroglycerine (NTG). In both models, the activation of the trigeminovascular system and induction of neuroinflammatory responses, key components of migraine pathophysiology, are observed. In this study, we conducted a comparative analysis of these two rat models of migraine: one induced by a single acute topical application of KCl onto the dura mater, and the other by intravenous injection of NTG, administered either as a single acute dose or repeatedly every other day over 9-days. Behavioral assessments were focused on evaluating migraine-associated symptoms, including facial mechanical allodynia and ptosis. Facial allodynia was quantified using von Frey filament stimulation and withdrawal scoring. Ptosis was evaluated using an eye closure score. In both models, we observed a significant increase in scores on Day 1, indicating the presence of acute facial hypersensitivity. In the NTG model, this effect was maintained on Days 5 and 9 following repeated NTG administrations, suggesting persistent sensitization. The KCl-induced model induced by a single application produced a transient response with allodynia confined to the acute phase. Ptosis, an indicator of autonomic dysfunction, was observed in both models, with the magnitude and consistency of ptosis being notably greater in the NTG group, aligning with clinical reports of autonomic symptoms in chronic migraine patients. Overall, our findings demonstrate that both the KCl and NTG models effectively replicate key features of migraine, while differing in duration and severity of symptoms. The KCl model is therefore best suited for investigating acute mechanisms related to

migraine with aura and potential treatments, and the NTG model more closely replicates features of chronic migraine without aura, including sustained sensitization and autonomic symptoms. Mechanism of action and intended clinical applications of the investigational compound should be seriously considered when selecting the relevant and appropriate validated preclinical animal model of migraine.

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## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.12/K2

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** National Natural Science Foundation of China NO.82222020  
National Natural Science Foundation of China NO.31825013

**Title:** Tg-sp5c-pbn pathway contributes to trigeminal neuropathic pain

**Authors:** \*J. WANG, L. SUN, X. LI, X. LIN, J. DENG;  
Fudan Univ., Shanghai, China

**Abstract:** Trigeminal neuropathic pain (TNP) is a severe form of orofacial pain characterized by recurrent brief unilateral electric shock-like pain triggered by innocuous stimuli. The efficacy of current drug treatment for TNP is limited, indicating the importance of fully understanding the underlying mechanisms of TNP. Since parabrachial nucleus (PBN) neuron activation was reported in inflammatory pain and neuropathic pain, we aim to identify whether PBN neurons and related circuits contribute to TNP. We applied constriction injury of the infraorbital nerve (CION) model to mimic the TNP, confirmed PBN Tac1 and Sp5C Tac1 neurons are involved through c-fos staining and RNAscope *in situ* hybridization, and evaluated their roles by monitoring the alterations in mechanical and thermal threshold in the whisker pad before and after treatment till day 14 after CION in transgenic reporter mice. We identified inhibition of PBN Tac1 neurons, which receive inputs from Sp5C Tac1 neurons attenuated the TNP development. Moreover, inhibition of Sp5C PBN projection neurons, which receive input from the trigeminal ganglion (TG), alleviated the mechanical and thermal allodynia in TNP mice. Also, chemogenetic activation of Sp5C GABAergic neurons hindered TNP development. Thus, our study discovered two pathways participating in TNP development, the Sp5C<sup>GABA</sup>-Sp5C<sup>Tac1</sup>-PBN<sup>Tac1</sup> and the TG-Sp5C<sup>Tac1</sup>-PBN<sup>Tac1</sup>, and sheds light on novel therapeutic targets for TNP treatment.

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## **Poster**

## **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.13/K3

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** R01NS072497 (PI: Arakaki)  
R01MH110438 (PI: Vasudevan)  
S10MH133643 (PI: Vasudevan)

**Title:** Selective vulnerability of GABAergic neurons in chronic migraine

**Authors:** \*K. HOSSAIN<sup>1</sup>, T. CHUONG<sup>1</sup>, E. ABAD<sup>1</sup>, J. LIN<sup>1</sup>, C. XIA<sup>2</sup>, X. ARAKAKI<sup>2</sup>, A. VASUDEVAN<sup>1</sup>;

<sup>1</sup>Angiogenesis & Brain Develop. Laboratory, Neurosciences, <sup>2</sup>Cognition and Brain Integration Laboratory, Dept. of Neurosciences, Huntington Med. Res. Inst. (HMRI), Pasadena, CA

**Abstract:** Abstract: Migraine is the fifth leading cause of neurological disability and has a strong genetic component. Previous linkage studies have identified a candidate migraine susceptibility locus on chromosome Xq24-28, which harbors several GABAA receptor subunit genes (GABRE, GABRA3, GABRQ). Despite its inhibitory role in the central nervous system, the contribution of the GABAergic system to migraine pathophysiology remains insufficiently understood. This study aims to elucidate the role of GABAergic neurons in chronic migraine using established rodent models. Chronic migraine was induced by repeated intraperitoneal administration of nitroglycerin (NTG, 10 mg/kg), a validated migraine trigger, every other day over a nine-day period. Control animals received an equivalent volume of saline. Mechanical hypersensitivity, a hallmark of migraine-associated allodynia, was assessed using von Frey filaments before and after NTG treatment. NTG-treated animals exhibited a progressive increase in mechanical sensitivity compared to controls, consistent with the development of a chronic migraine-like state. Notably, a selective reduction in GABAergic neurons was observed in male, but not female, NTG-treated mice, specifically within the neocortex, amygdala, hippocampus, and locus coeruleus. This loss of GABAergic neurons was accompanied by elevated expression of  $\Delta$ FosB, a marker of sustained neuronal activation, and increased apoptotic signaling indicated by active caspase-3 staining. Furthermore, male chronic migraine mice showed upregulation of stress-related neuropeptides, including PACAP and its receptor PAC1, as well as downstream effectors BDNF and TrkB. Gene expression analysis revealed downregulation of GABA signaling components in the choroid plexus of the fourth ventricle, including aberrant overexpression of the chloride cotransporter NKCC1. These findings reveal a male-specific vulnerability of GABAergic neurons in chronic migraine and suggest a sex-dependent divergence in the underlying pathophysiological mechanisms. This highlights the need for sex-specific approaches to migraine research and therapeutic development.

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## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.14/K4

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Effects of Olcegepant, Sumatriptan, and Ibuprofen on Migraine-Like Behavior Induced by Repetitive Restraint Stress in Mice

**Authors:** \*S. NEMATGORGANI;  
Univ. of Texas at Dallas, Richardson, TX

**Abstract: Background:** Stress is the most reported trigger for migraine, with approximately 70% of individuals reporting it as a trigger for their attacks. Repeated stress potentially lowering the threshold for nociceptor activation and increasing the likelihood of episodic migraine progression to chronicity. Given this, further research is needed to find effective treatments for stress-induced migraine headaches. Previous studies have demonstrated the benefits of acute migraine therapy in the management of migraine attacks, and they may protect against migraine chronification. In this study we aim to determine whether ibuprofen, sumatriptan and olcegepant attenuate stress-induced hypersensitivity and priming to subthreshold doses of the nitric oxide donor SNP (sodium nitroprusside). **Methods:** Female CD1 mice were exposed to 2 hours of restraint stress for 3 consecutive days. Twenty-four hours after restraint stress, the first administration of sumatriptan (0.6 mg/kg, subcutaneous) and olcegepant (1 mg/kg, intraperitoneal) was performed. These injections were repeated for sumatriptan on Day 3, while olcegepant was injected on Day 2, and Day 3. Additionally, Ibuprofen (200 mg/kg, intraperitoneal) was administered 24 hours post-stress. Periorbital withdrawal thresholds using von Frey filaments and facial grimace scores were measured following stress. In addition, to assess hyperalgesic priming, animals received an injection of SNP (0.1 mg/kg) once they returned to baseline following stress. **Results:** We showed that repeated restraint stress induces periorbital hypersensitivity in mice 24 hours after stress. Following restraint stress, olcegepant and sumatriptan injections on day 1 decreased facial hypersensitivity 1 h after the injection, while the effect of ibuprofen was significant at 1 hour, 3 hours and 5 hours post-injection. Responses to subthreshold doses of SNP in primed animals were not attenuated significantly by Ibuprofen and sumatriptan, but olcegepant significantly reduced SNP-induced responses in stressed animals 24 hours post-SNP administration. The grimace score did not decrease significantly in the Ibuprofen and sumatriptan group. However, olcegepant led to a significantly lower grimace score on day 1 post-stress, observed at 1 hour and 5 hours post-injection. **Conclusion:** We showed that restraint stress can cause migraine-like behaviors that are responsive to several migraine therapeutics. These data further validate this model as being translationally relevant for testing migraine therapeutics and they provide insight into the mechanisms by which stress causes behavioral features consistent with migraine.

**Disclosures:** S. Nematgorgani: None.

## Poster

### PSTR219: Headache, Migraine, and Trigeminal Circuits

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.15/K5

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Study of the effects of psilocybin in three rat preclinical models of migraine, insights from the trigeminovascular system

**Authors:** O. GUILLEMOT-LEGRIS<sup>1</sup>, I. SHAND<sup>1</sup>, J. FEATHERSTONE<sup>1</sup>, M. BARYLA<sup>2</sup>, J. ARAUJO<sup>3</sup>, M. DUXON<sup>1</sup>, \*K. R. WALKER<sup>1</sup>, C. TAYLOR<sup>1</sup>, G. A. HIGGINS<sup>3</sup>;

<sup>1</sup>Transpharmation Ltd, Sandwich, United Kingdom; <sup>2</sup>Transpharmation Ltd, Olsztyn, Poland;

<sup>3</sup>Transpharmation Ltd, Fergus, ON, Canada

**Abstract:** Migraine is a complex disorder the aetiology of which is still not fully understood. It is characterised by recurring headache episodes that greatly affects patients' quality of life. Even though migraine clinical manifestations can vary greatly, its pathophysiology has been found to involve complex processes implicating neurological and vascular mechanisms. One structure thought to be central in these processes is the trigeminovascular system. Treatment options are still limited to drugs aimed at decreasing the reoccurrence of episodes or abortive drugs aimed at decreasing the severity and length of an episode when it already started. Adding to the complexity of the disease, some patient will not respond to classical treatments. Recently, psychedelics have been receiving renewed attention as potential treatment for several complex diseases that are difficult to tackle with current treatment options. Interesting effects were shown in several models of neuropathic pain and psychedelics effects are also being studied in the fields of anxiety and depression. In the clinic, psilocybin has been shown to be effective in migraineurs as it decreased migraine frequency and severity in participants. Interestingly, however, psilocybin administration in healthy volunteers was shown to induce transient headaches. As this compound could represent an interesting treatment avenue we wanted to assess, from a more mechanistical standpoint, the effects of psilocybin in three preclinical rat models of migraine. We used the glyceryl trinitrate (GTN), the calcitonin gene-related peptide (CGRP), and the pituitary adenylate cyclase-activating polypeptide 38 (PACAP-38) models to interrogate specific pathophysiological pathways independently and evaluate the effects of psilocybin in each. In these models, we assessed mechanical hyperalgesia using von Frey filaments in the periorbital and plantar regions. In all three models, psilocybin was able to significantly reduce mechanical hyperalgesia in both areas tested. Finally, we assessed the effects of psilocybin on the levels of several inflammatory markers (cytokines and chemokines) and neurotrophic factors in the plasma, brainstem, and trigeminal ganglia. This work allowed us to assess the effects of psilocybin in vivo on three mechanistically distinct migraine models while characterising changes induced in key markers of the trigeminovascular system. While the specific distinction between acute psychotropic effects and longer neuroplastic changes remains to be further deciphered, this data paves the way for a better understanding of the acute effects of psilocybin in migraine.



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**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.16/K6

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** SECIHTI Grant CBF 2023-2024/3878

**Title:** Acute and chronic analgesic effects of cannabigerol in mice with trigeminal pain

**Authors:** \*G. N. QUIÑONEZ-BASTIDAS<sup>1</sup>, G. G. ESCOBAR-LÓPEZ<sup>1</sup>, M. CASTILLO<sup>2</sup>;  
<sup>1</sup>Neuropharm. and Pain Laboratory, Res. Department, CIDOCS, Univ. Autónoma de Sinaloa, Culiacán, Mexico; <sup>2</sup>ICAN GREEN S. A. de C. V, Ciudad de México, Mexico

**Abstract:** Introduction: Trigeminal pain is a disabling condition commonly treated with anticonvulsant drugs which are associated with several side effects. No new medications have been released to the market in recent years for the treatment of trigeminal pain. Recent reports have indicated that cannabigerol (CBG) is a non-psychoactive phytocannabinoid with antinociceptive properties. The aim of this study was to investigate the efficacy of CBG in neuropathic, nociplastic, and nociceptive trigeminal pain in mice. Material and methods: Female ICR/CD1 mice (20-25 g) were injected with 20 µl of 2.5% formalin into the upper lip of mice to induce a nociceptive behavior in face and a sustained sensitization in paws. Trigeminal neuropathy was induced by chronic constriction injury in the infraorbital nerve. Allodynia and sensitization were evaluated by von Frey filaments. Experiments were conducted in accordance with the Ethics Committee for the Use of Animals in Pharmacological and Toxicological Testing and the Guidelines on the Ethical Standards for Investigation of Experimental pain in Animals. Results: The acute intraperitoneal administration of CBG (10 and 32 mg/kg) reduced the nociceptive behavior. Moreover, CBG (100 mg/kg) attenuated allodynia, likewise, the chronic administration of CBG (10 and 32 mg/kg) decreased the sustained sensitization in both paws of animal. Conclusion: Taken together the data suggest that acute and chronic administration of CBG reduces the trigeminal pain behavior, highlighting its effectiveness in inflammatory, neuropathic, and nociplastic types of pain.

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**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.17/K7

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH grant UL1TR001881  
NIH grant CA196263  
NIH grant U54HL119893  
NIH grant UG3NS128148

**Title:** Cannabinoid actions on sensitized dural nociceptors in a mouse migraine-like pain model

**Authors:** Y. KITAOKA<sup>1</sup>, K. L. WHYLAND<sup>1</sup>, Z. LI<sup>1</sup>, K. KOSHIKA<sup>2</sup>, T. YAMAMOTO<sup>3</sup>, Y. MULPURI<sup>4</sup>, E. WHITEHOUSE<sup>1</sup>, R. MURALI<sup>1</sup>, P. CHABRIA<sup>1</sup>, L. P. LE<sup>1</sup>, P. AHMADI<sup>1</sup>, J. SHAFI<sup>1</sup>, L. ANDREASYAN<sup>1</sup>, H. SELTZMAN<sup>5</sup>, \***I. SPIGELMAN**<sup>1</sup>;

<sup>1</sup>Lab. of Neuropharmacology, Section of Biosystems & Function, Sch. of Dent., UCLA, Los Angeles, CA; <sup>2</sup>Dent. Anesthesiol., Tokyo Dent. college, Tokyo, Japan; <sup>3</sup>Dent. Anesthesiol., Niigata Univ., Niigata, Japan; <sup>4</sup>Bluestone Ctr. for Clin. Res., NYU Col. of Dent., New York, NY; <sup>5</sup>Seltzman LLC, Raleigh, NC

**Abstract:** Migraine is a debilitating neurological disorder affecting ~15% of the global population, with higher prevalence in females. Cannabinoids targeting Gi/o-coupled CB1 and CB2 receptors alleviate migraine symptoms but are limited clinically due to CNS side effects mediated by CB1Rs. To overcome this, we developed peripherally restricted cannabinoid receptor agonists (PRCBs) that do not cross the blood-brain barrier, including PrNMI (4-{2-[(1E)-1-[(4-propylnaphthalen-1-yl)methylidene]-1H-inden-3-yl]ethyl}morpholine), which exhibits potent analgesic effects in preclinical chronic pain models with minimal CNS side effects or tolerance. Here, we used non-invasive supradural injection of pH 6.0 saline in 5-week-old female C57BL/6J mice to induce migraine-like pain symptoms of periorbital cutaneous allodynia, which causes priming to normally subthreshold pH 7.0 saline stimulation of the dura (at 3 days) following resolution of the initial pain symptoms. Co-administration of PrNMI (5  $\mu$ M) with pH 6.0 saline at the time of the initial supradural injection completely prevented both the onset of allodynia and the development of latent sensitization. These preventative effects were abolished when the CB1R-selective inverse agonist 18A (20  $\mu$ M) or the CB2R-selective inverse agonist SR144528 (20  $\mu$ M) were co-administered. Surprisingly, supradural co-administration of the potent CB2R-selective agonist RNB61 (5  $\mu$ M) with pH 6.0 saline did not prevent the acid-induced allodynia or latent sensitization. Furthermore, post-treatment of PrNMI with pH-7.0 saline did not prevent latent allodynia. Electrophysiological recordings were conducted from fluorogold-labeled dural-projecting trigeminal ganglion neurons (dTGs), acutely isolated 3 days after supradural injection of pH 6.0 or pH 7.4 saline with fluorogold. In pH 6.0-treated mice, significantly greater depolarizing responses to acid stimulation were observed ( $p = 0.04$ ), indicating increased excitability. PrNMI (1  $\mu$ M) significantly reduced acid responses in dTGs from pH 7.4-treated animals ( $p = 0.032$ ), but had no such effect in neurons from pH 6.0-treated animals, suggesting a loss of CB1R efficacy following acid-induced sensitization. Furthermore, in recordings from dTGs of pH 7.4-treated mice, RND61 (1  $\mu$ M) had no inhibitory

effect on acid-induced depolarizations. These findings indicate that PrNMI prevents acid-induced sensitization by co-activating neuronal CB1Rs and non-neuronal CB2Rs. CB2R activation alone is insufficient, and once sensitized, combined CB1R/CB2R activation loses efficacy.

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## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.18/K8

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH Grant RF1NS137467

**Title:** Meningeal lymphatics and CSF solute loops regulate trigeminal pain resolution

**Authors:** \*J.-F. CHEN<sup>1</sup>, Q. CHANG<sup>2</sup>;

<sup>1</sup>Univ. of Southern California (USC), Los Angeles, CA; <sup>2</sup>USC, Los Angeles, CA

**Abstract:** The cerebrospinal fluid (CSF) offers a non-synaptic communication route between the central nervous system (CNS) and the peripheral trigeminal ganglion (TG), but the regulatory mechanisms remain poorly understood. Here, we discovered in a mouse model of migraine that distinct meningeal lymphatics and CSF solute loops control trigeminal pain sensitization and resolution, respectively. Our whole brain clearance and imaging revealed that basal meningeal lymphatics are proximally localized to TG, where CSF flows through trigeminal neurons that uptake CSF solutes. Lymphatic loss- and gain-of-function demonstrated that migraine induction impairs basal lymphatic endothelial cell (LEC) morphology and drainage functions, causes CSF solute accumulation, activates trigeminal neurons leading to migraine-like behaviors. Mechanistic studies showed that lymphatic dysregulation induced the accumulation of CSF solutes, including TG inhibitor and TG activator. In contrast to CGRP inhibition on lymphatics leading to a pathological positive feedback loop, TG activation solutes promote lymphatic function and pain resolution by forming a self-weakening negative feedback loop. Together, meningeal lymphatic-CSF solutes form two distinct feedback loops to mediate brain-TG crosstalk controlling trigeminal pain progression and resolution, providing potential targets for therapeutic strategies.

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## **Poster**

## **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.19/K9

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** University of Toronto Centre for the Study of Pain Pain Scientist  
Scholarship  
Ontario Graduate Scholarship

**Title:** The Glymphatic System in Trigeminal Neuralgia: Associations with Surgical Response

**Authors:** \*A. WOLFENSOHN<sup>1</sup>, J. LI<sup>1</sup>, D. JORGENS<sup>4</sup>, T. H. LATYPOV<sup>6</sup>, P. SRISAIKAEW<sup>5</sup>, T. AGYEKUM<sup>7</sup>, E. ADHAMIDHIS<sup>2</sup>, M. HODAE<sup>3</sup>;

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**Abstract:** Trigeminal neuralgia (TN) is a chronic neuropathic pain disorder that causes severe facial pain. TN is often responsive to neurosurgical interventions, making it a useful model for exploring the differences between pain and pain-free states at the neurological level. The glymphatic system (GS), a recently identified waste clearance pathway in the brain, has been implicated in aging and neurodegeneration, yet its role in chronic pain remains understudied. As a result, we assessed GS function in TN using two magnetic resonance imaging (MRI)-based markers: diffusion tensor imaging along the perivascular space (DTI-ALPS) and choroid plexus volume (CPV). We hypothesized that TN patients will exhibit reduced GS function, indicated by lower DTI-ALPS and increased CPV compared to healthy controls (HCs). We also predicted that GS dysfunction will normalize following successful surgical pain relief. T1-weighted and diffusion MRI data was collected from 295 surgically naive TN patients and 295 age- and sex-matched HCs, acquired locally and through external databases. A subset of 80 TN participants undergoing Gamma Knife (GK) radiosurgery underwent additional imaging 6 to 12 months postoperatively to evaluate any changes following successful or unsuccessful surgical pain relief. Preliminary results from a subset of 50 TN and 50 HC participants indicated significantly reduced DTI-ALPS indices in TN patients compared to HCs in both hemispheres (left:  $1.25 \pm 0.16$  vs.  $1.45 \pm 0.38$ ,  $p < 0.001$ , Cohen  $d = 0.71$ ; right:  $1.24 \pm 0.13$  vs.  $1.43 \pm 0.34$ ,  $p < 0.001$ , Cohen  $d = 0.72$ ), suggesting a likely association between TN and worsened GS efficacy. Ongoing analyses include CPV computation from preprocessed T1-weighted images using a Gaussian Mixture Model-based approach, as well as statistical analyses to integrate GS-related metrics with sex, age, and treatment response. Overall, our work has the potential to clarify the interplay between glymphatic function and chronic pain disorders like TN, advancing our understanding of chronic pain pathophysiology and elucidating how pain may affect systemic brain health. These findings may also contribute to the development of objective, neuroimaging-based biomarkers for TN and other conditions.

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**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.20/K10

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** R01 NS094413

**Title:** Brain Entropy Reflects Rigid Neural Processing in Migraine

**Authors:** \*M. SABERI, D. KIM, X. HU, A. DASILVA;  
Univ. of Michigan, ANN ARBOR, MI

**Abstract:** Migraine is a common neurological disorder characterized by recurrent headache attacks. Understanding brain dynamics in migraine may provide insights into the cognitive and emotional dysfunctions frequently reported by patients. Brain entropy, a measure of signal complexity, reflects the flexible and rigid neural processing. This study aimed to examine regional neural adaptability in individuals with migraine and to assess the acute effects of migraine attacks. We collected resting-state fMRI from individuals with episodic migraine (n=25), chronic migraine (n=15), and healthy controls (n=26). After standard preprocessing, voxel-wise brain entropy maps were computed using the sample entropy algorithm. Linear regression was performed at each voxel, with entropy as the dependent variable, group as the predictor, and age and sex as covariates. Significant clusters were identified following multiple comparisons correction. We identified four brain regions with significantly reduced entropy in migraine patients, most prominently in those with chronic migraine: the occipital cortex (OC), right supramarginal gyrus and superior parietal lobule (rSMG+rSPL), precuneus and posterior cingulate cortex (PCu+PCC), and medial prefrontal cortex (mPFC). Entropy was transiently elevated during the ictal phase and declined over time in the rSMG+rSPL, indicating temporary restoration of neural complexity in sensory integration regions. Lyapunov analysis indicated that this temporary complexity increase was driven by chaotic (non-random) dynamics. Our findings indicate that migraine is associated with rigid neural processing in brain regions linked to visual perception, sensory integration, self-referential processing, and emotion regulation. Moreover, migraine attacks may facilitate a transient escape from this rigidity, especially in sensory integration areas, through a compensatory increase in neural complexity.

**Disclosures:** M. Saberi: None. D. Kim: None. X. Hu: None. A. Dasilva: None.

**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.21/K11

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Pacap and Related Neuropeptides: Distinct and Overlapping Signaling in In Vitro Models

**Authors:** \***M. A. X. TOLLENAERE**<sup>1</sup>, **R. MADSEN**<sup>2</sup>, **M. AMBJORN**<sup>3</sup>, **A. A. ASUNI**<sup>4</sup>;

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<sup>3</sup>Functional and Cell. Pharmacol., H Lundbeck A/S, Valby, Denmark; <sup>4</sup>Neurosci., H Lundbeck, Copenhagen, Denmark

**Abstract:** Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP), Calcitonin Gene-Related Peptide (CGRP), and Vasoactive Intestinal Peptide (VIP) are pleiotropic neuropeptides implicated in migraine pathophysiology. Monoclonal antibodies targeting PACAP and CGRP have shown clinical efficacy in migraine trials. PACAP and VIP share structural features and activate the GPCRs PAC1R, VPAC1R, and VPAC2R, yet differ in receptor selectivity, tissue distribution, and signaling dynamics. CGRP, acting through a distinct receptor complex, exhibits partial overlap in downstream effects. Our research investigates functional crosstalk and signaling interplay among these neuropeptides in diverse in vitro cell systems. By leveraging pharmacological tools and cellular assays, we aim to build a broader understanding of neuropeptide network interactions and their relevance to disease mechanisms and therapeutic targeting in headache disorders.

**Disclosures:** **M.A.X. Tollenaere:** A. Employment/Salary (full or part-time): H. Lundbeck A/S.

**R. Madsen:** A. Employment/Salary (full or part-time): H. Lundbeck A/S. **M. Ambjorn:** A.

Employment/Salary (full or part-time): H. Lundbeck A/S. **A.A. Asuni:** A. Employment/Salary (full or part-time): H. Lundbeck A/S.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.22/K12

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** Internal Grant

**Title:** Post-prandial glucose dysregulation and glycemic phenotyping in chronic migraine

**Authors:** \***K. BILLS**<sup>1</sup>, **C. SMALL**<sup>2</sup>, **D. SANT**<sup>3</sup>;

<sup>1</sup>Noorda Col. of Osteo. Med., Provo, UT; <sup>2</sup>Psychology, Noorda Col. of Osteo. Med., Provo, CA;

<sup>3</sup>Biomed. Sci., Noorda Col. of Osteo. Medic, Provo, UT

**Abstract:** Emerging evidence suggests that a metabolic mismatch between cerebral energy demand and supply may be a contributing factor to the onset of migraine. Studies have drawn connections between migraine and conditions such as hypoglycemia, fasting, GLUT1 transporter deficiency, insulin resistance, and diabetes, highlighting the role of metabolic dysregulation in migraine susceptibility. Exploring plasma glucose levels in individuals with migraine may provide deeper insights into this metabolic interface, offering potential avenues for personalized migraine treatments targeting glucose regulation. Data from chronic migraine patients (>15 headache days/month) were analyzed using continuous glucose monitoring (CGM) (n=108) and oral glucose tolerance tests (GTT) (n=169). CGM was analyzed and compared to 24 healthy controls. Compared to age and gender-matched standards of normal GTT response, those with chronic migraine had significant deviation at two hours ( $p<0.0001$ ), indicating post-prandial dysregulation. CGM data also showed that migraine subjects had greater glucose variability, including greater day-to-day (MODD) ( $p=0.0084$ ) and within-day (CONGA24) glycemic variability ( $p=0.00078$ ), and inter and intraday standard deviation during waking hours ( $p=0.0049$ ,  $p=0.0034$ , respectively). Measures of post-prandial glycemic dysregulation including mean amplitude of glycemic excursion (MAGE), mean glucose excursion (MGE), and post-prandial glucose recovery time (PGRT) showed increases in post-prandial excursions and their amplitudes in migraine subjects. Despite no significant changes in recovery time, subjects with migraine had greater AUC values in the post-prandial period, suggesting reactive hypoglycemia. Due to the non-normal distributions of our migraine subjects results on a variety of measures, we clustered subjects into three groups based on outcomes on interday SD, CONGA24, and mean glucose using k means. This clustering identified groups of subjects with (1) high variability, high average glucose, yet normal OGTT response, (2) normal variability and GTT response, yet high average glucose and post prandial amplitude, and (3) normal variability and average glucose, but a blunted GTT response that trends hypoglycemic at hour 3. These identified phenotypes highlight distinct glucose regulation patterns, suggesting different migraine-associated metabolic profiles. Further research will explore factors contributing to these phenotypes and their implications for migraine pathogenesis. These findings support the potential for targeted migraine treatments informed by glucose dysregulation patterns.

**Disclosures:** K. Bills: None. C. Small: None. D. Sant: None.

## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.23/K13

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** Canada Graduate Scholarship - Doctoral Program (CGS D)

**Title:** Reversible neural signatures of pain in trigeminal neuralgia identified with ensemble methods and structural brain imaging

**Authors:** \*J. Li<sup>1</sup>, T. H. LATYPOV<sup>3</sup>, D. JORGENS<sup>4</sup>, P. SRISAIKAEW<sup>5</sup>, E. ADHAMIDHIS<sup>1</sup>, M. HODAIE<sup>2</sup>;

<sup>1</sup>Inst. of Med. Sci., <sup>2</sup>Neurosurgery, Toronto Western Hosp., Univ. of Toronto, Toronto, ON, Canada; <sup>3</sup>Neurosciences and Mental Hlth., The Hosp. for Sick Children, Toronto, ON, Canada; <sup>4</sup>Krembil Res. Inst., <sup>5</sup>Krembil Res. Institute, Toronto Western Hosp., Univ. Hlth. Network, Toronto, ON, Canada

**Abstract:** Imaging derived brain biomarkers for chronic pain have been limited. Trigeminal neuralgia (TN) is a debilitating neuropathic facial pain condition that can be effectively treated with surgery. After pain-relieving surgery, brain abnormalities in TN can normalize. However, the scale and dynamics of this normalization process are unclear. Machine learning (ML) can aid in the identification of brain imaging biomarkers to explain the neural underpinnings of TN. Thus, we collected MRIs of 117 local TN patients who underwent pain-relieving surgery and 1068 healthy controls (HC) from various external, geographically distinct databases. TN patient MRIs were collected within 6 months before surgery and 6-10 months following surgery. We then optimized an ensemble of support vector classifiers to differentiate between the 117 TN patients and 834 HC. We employed ML best practices, such as interpretable models and external validation, to reproducibly and objectively identify a structural pain signature associated with TN. Before pain-relieving surgery, using this pain signature, the ensemble could differentiate between 117 patients and a held-out set of age- and sex-matched HC with 99% accuracy ( $AUROC = 0.999$ ). After pain relief, 28 TN surgical responders, a significant proportion, were reclassified as HC (chi-squared  $q < 0.001$ ). Underlying prediction probabilities showed that 96/117 TN responders (82%) shifted towards a healthier brain phenotype after pain relief (Wilcoxon signed-rank  $q < 0.001$ ). Nonlinear decomposition of the data illustrated clear and distinct clustering of pre-surgery TN and HC, with post-surgery TN in between, but linear decomposition did not. Therefore, this normalization process is likely nonlinear in nature. Shapley values determined that this pain signature was primarily comprised of subcortical cognitive regions. The most important feature was the volume of the left accumbens area, with larger volumes being more predictive of TN. Other cognitive regions part of the pain signature included the ventral diencephalon, basal ganglia, thalamus, hippocampal and amygdala areas, and ventricular regions. In conclusion, our longitudinal study identified a novel, reversible pain signature unique to TN. We illustrated that brain structure alone is enough for ML to distinguish between TN and being pain-free, and that recovery from neuropathic pain may be detectable within a year of pain-relieving surgical intervention. These findings provide a foundation for mechanistic and ML-based studies of subcortical regions in TN, many of which are related to cognition, and support the potential for ML to augment clinicians.

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## **Poster**

### **PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM



**Program #/Poster #: PSTR219.24/K14**

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Photophobia-focused multidimensional evaluation galcanezumab in migraine: analysis through upsis-12 and clinical measures

**Authors:** \***K. BIRISIK**<sup>1</sup>, **A. SAHIN**<sup>2</sup>, **P. YALINAY DIKMEN**<sup>2</sup>, **E. ILGAZ AYDINLAR**<sup>2</sup>;  
<sup>2</sup>Neurol., <sup>1</sup>Acibadem Mehmet Ali Aydinlar Univ., Istanbul, Turkey

**Abstract:** Galcanezumab, a humanized monoclonal antibody targeting calcitonin gene-related peptide (CGRP), is widely used for the treatment of migraine. This study aimed to evaluate its clinical efficacy from a multidimensional standpoint, with particular emphasis on photophobia, as well as treatment outcomes and patient-specific comorbidities. Additionally, the study explored the relationship between treatment outcomes and patient-specific comorbidities. In this retrospective cohort, patients received a 240 mg loading dose of galcanezumab followed by monthly 120 mg subcutaneous injections over three months. Clinical assessments included the Turkish version of the 12-Item Utah Photophobia Symptom Impact Scale (UPSIS-12), the Headache Impact Test (HIT-6), the Migraine Disability Assessment (MIDAS), the Beck Anxiety and Depression Inventories, and the Allodynia Symptom Checklist. Outcomes were evaluated across four visits, focusing on changes in headache frequency, pain severity, analgesic use, and associated sensory symptoms including phonophobia and osmophobia. Among 77 patients (42 females, 5 males), 47 completed all scheduled visits and were included in the final analysis (mean age: 39 years; range: 18-61). Episodic migraine without aura was the most prevalent subtype, followed by chronic migraine and migraine with aura. Repeated measures ANOVA demonstrated a significant reduction in UPSIS-12 scores over time ( $p < 0.001$ ), with the most pronounced improvements between Visits 1 and 3-4. Significant reductions were also observed in headache days, pain intensity, analgesic consumption, HIT-6, MIDAS, allodynia, and mood disturbance scores. Patients with allergic comorbidities experienced greater photophobia improvement, whereas those with sleep-related disorders or adverse effects derived less benefit (Mann-Whitney U,  $p < 0.05$ ). Galcanezumab conferred therapeutic benefits across multiple migraine domains. The use of UPSIS-12 enabled a nuanced assessment of both ictal and interictal photophobia, offering insights into underlying neurophysiological mechanisms. By targeting CGRP, galcanezumab may modulate the pathological interplay between intrinsically photosensitive retinal ganglion cells (ipRGCs), the trigeminovascular system, and hyperexcitable thalamocortical circuits. To our knowledge, this is the first study to apply UPSIS-12 longitudinally in a treatment-monitoring context, providing a clinically scalable, photophobia-focused framework for migraine care and research.

**Disclosures:** **K. Birisik:** None. **A. Sahin:** None. **P. Yalinay Dikmen:** None. **E. Ilgaz Aydinlar:** None.

**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.25/K15

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** DOD W81XWH-15-1-0679  
DOD W81XWH-09-1-0526  
DOD W81XWH-17-1-0457

**Title:** Migraine symptoms and visual cortex thickness are significantly reduced following a 1-month low glutamate diet in veterans with Gulf War Illness

**Authors:** \*H. CROWDER<sup>1</sup>, D. T. BOOKER<sup>2</sup>, S. M. DRAGOI<sup>2</sup>, J. N. BARANIUK<sup>3</sup>, K. F. HOLTON<sup>4</sup>, A. S. VANMETER<sup>1</sup>;

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<sup>3</sup>Georgetown Univ., Bethesda, MD; <sup>4</sup>Depts. of Hlth. Studies and Neurosci., American Univ., Washington, DC

**Abstract:** Gulf War Illness (GWI) is a chronic condition that affects approximately one out of four veterans that served in the 1990-1991 Gulf War. GWI is characterized by various musculoskeletal, gastrointestinal, and neurologic symptoms including migraines, which are thought to be connected to central nervous system dysfunction due to neurotoxic exposures during the war. We report here on two studies examining the visual cortex in veterans with GWI, based on prior studies of migraineurs. High resolution T1w images (MPRAGE, 1mm3) were collected in both studies. Scans were first denoised using ANTs DenoiseImage (Study 1), then quality control was run using MRIQC and visual confirmation. Scans were segmented using CAT12. Visual quality control was performed on the surface data, and those with a Quartic Mean Absolute Z-Score  $\geq 2$  were excluded. Cortical thickness differences were analyzed in CAT12 using an independent two-sample t-test for the first study and a paired t-test for the second study. Our first study examined the differences in cortical thickness in the visual cortex among individuals with GWI, as compared to healthy controls (HC). Data were collected for 116 adults (age= 46 (11), 74% male); of these, there were 83 GWI (age= 44 (17), 64% male) participants in the sample, and 33 HC (age=47 (7), 78% male). T1w images were collected for 112 of these participants, but 39 subjects were excluded due to poor scan quality. In this first study, a significantly higher proportion of the veterans with GWI reported experiencing migraines ( $X^2(1, N = 114) = 20.647, p < 0.001$ ), as compared to HC. The GWI subgroup also had a significantly thicker right visual cortex (V3) than the HC subgroup (pFDR-corr=0.017). The second study piloted a dietary intervention for forty veterans with GWI (age= 54 (6), 73% male). T1w images were collected for 30 of these participants. Scans were excluded due to poor scan quality (n=4) or missing the post-diet scan (n=1). A significant reduction in cortical thickness was observed after one-month on the low-glutamate diet, in both left (pFDR-Corr < 0.001) and right (pFDR-Corr < 0.04) visual cortices (V2). Additionally, we found a significant correlation between the reduction of headache symptoms and reduced cortical thickness in both left (p = 0.029) and right (p = 0.007) visual cortices. Together, these findings contribute to a body of work implicating glutamatergic excitotoxicity and neuroinflammation as potential mechanisms underlying both migraine and GWI. Ongoing analyses, including a larger clinical trial, are underway to further explore this relationship.

**Disclosures:** H. Crowder: None. D.T. Booker: None. S.M. Dragoi: None. J.N. Baraniuk: None. K.F. Holton: None. A.S. VanMeter: None.

**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.26/K16

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** National Institute of Dental & Craniofacial Research of the National Institutes of Health, Award Number DE027414  
National Institutes of Health's National Center for Advancing Translational Sciences, grant UM1TR004405

**Title:** Chronic TMD pain clinical characteristics fluctuations regarding pain presence and laterality

**Authors:** \*S. DUFFY<sup>1</sup>, A. HAGSTRÖM<sup>2</sup>, R. NUWAILATI<sup>3</sup>, L. HUFFMAN<sup>1</sup>, E. J. MOANA-FILHO<sup>4</sup>;

<sup>1</sup>Diagnos. Biol. Sci., Univ. of Minnesota: Twin Cities, Minneapolis, MN; <sup>2</sup>Diagnos. Biol. Sci., Univ. of Minnesota, Twin Cities, Dept. of Diagnos. and Biol. Sci., Minneapolis, MN; <sup>3</sup>Diagnos. Biol. Sci., <sup>4</sup>Diagnos. and Biol. Sci., Univ. of Minnesota Sch. of Dent., Minneapolis, MN

**Abstract:** Chronic temporomandibular disorder (TMD) pain affects an estimated 12% of the US population, and it can substantially affect the quality of life of patients. It usually presents as a continuous, bilateral mild to moderate dull and achy pain over the jaw, that can fluctuate in intensity secondary to function or even without clear aggravating factors. There is currently limited knowledge about the frequency of these changes in chronic TMD pain clinical characteristic. To address this gap in knowledge, we collected data from 35 adult females diagnosed with chronic TMD pain subdivided as low- (n=24) and high- (n=11) impact pain over an 8-day period. Each participant was asked to complete daily rating surveys (DR01-07) every evening during 7-days before the initial visit plus another daily rating in the evening of the day of the initial study visit (V1), with a required minimum of four completed DR in this period. Each DR included questions about jaw pain presence and affected side to assess changes in jaw pain laterality. Jaw pain presence was defined as any pain reported by the participant in the jaw area during the day of DR completion (yes/no), while jaw pain laterality was defined as the side of the jaw reported as painful (left, right, bilateral, no pain). Pain laterality changes were determined by comparing the jaw pain side on a given day relative to the previous day. Results showed that both TMD-low and TMD-high individuals said yes for jaw pain presence at about 2/3 of days during the 8-day period (TMD-low median=71%, min=67%, max=83%; TMD-high median=73%, min=50%, max=90%). Regarding jaw pain laterality, both TMD-low and TMD-high individuals presented with side changes during the 8-day period at about 1/3 of days (TMD-low median=30%, min=0%, max=52%; TMD-high median=36%, min=0%, max=60%). These

results suggest that, while chronic TMD pain is usually described as a continuous bilateral jaw pain, patients do experience pain-free days, and they also note changes in which side of their jaw is affected by pain. Better understanding of chronic TMD pain clinical characteristics is expected to help development of improved human and animal experimental models to further investigate this condition's pathophysiology with better ecological validity.

**Disclosures:** **S. Duffy:** A. Employment/Salary (full or part-time): University of Minnesota: Twin Cities (School of Dentistry) Department of Diagnostic and Biological Sciences. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Dental & Craniofacial Research of the National Institutes of Health, National Institutes of Health's National Center for Advancing Translational Sciences. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Minnesota: Twin Cities (School of Dentistry). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Minnesota: Twin Cities (School of Dentistry). **A. Hagström:** A. Employment/Salary (full or part-time): University of Minnesota: Twin Cities (School of Dentistry). B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health (NIH). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Minnesota: Twin Cities (School of Dentistry). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Minnesota: Twin Cities (School of Dentistry). **R. Nuwailati:** A. Employment/Salary (full or part-time): University of Minnesota: Twin Cities (School of Dentistry) Department of Diagnostic and Biological Sciences. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health (NIH). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Minnesota: Twin Cities. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Minnesota: Twin Cities. **L. Huffman:** A. Employment/Salary (full or part-time): University of Minnesota: Twin Cities (School of Dentistry). B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health (NIH). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Minnesota: Twin Cities (School of Dentistry). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Minnesota: Twin Cities (School of Dentistry). **E.J. Moana-Filho:** A. Employment/Salary (full or part-time): University of Minnesota: Twin Cities. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health (NIH). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Minnesota: Twin Cities. E.

Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Minnesota: Twin Cities.

**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.27/L1

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Temporal dynamics of neuronal activities in the insular cortex during experimental tooth movement

**Authors:** \*K. KITANO<sup>1</sup>, M. KOBAYASHI<sup>2</sup>;

<sup>1</sup>pharmacology, Nihon Univ. Sch. of Dent., Chiyoda-ku, Tokyo, Japan; <sup>2</sup>Pharmacol., Nihon Univ. Sch. Dent., Chiyoda-Ku, Japan

**Abstract:** Orthodontic treatment causes pain and discomfort. The continuous mechanical force is applied to the periodontal ligament for orthodontic treatment, which induces inflammation in the periodontal ligament. We have demonstrated the changes in neuronal activities in the insular cortex using acute preparations. However, sequential changes during experimental tooth movement (ETM) for more than one week have yet not known. In this study, we chronically recorded the neural activities from the same neuron that responses to ETM by two photon microscopy. Thy1-GCaMP6s mice were put with a head post, and after detaching the temporalis muscle, cranial window made around the middle cerebral artery. A prism was implanted to the window. ETM was made by inserting the rubber between first and second molar. We succeeded to image neuronal activities chronically: we obtained from the same neuron of the same mouse at least for a week. The neuronal responses to electrical stimulation of the periodontal ligament show time the dependent changes during ETM. The time course of neuronal activities was almost parallel to that of the strength of nociception. These findings suggest that the change of neural activity in insular cortex reflects the pain induced by the orthodontic treatment.

**Disclosures:** K. Kitano: None. M. Kobayashi: None.

**Poster**

**PSTR219: Headache, Migraine, and Trigeminal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.28/L2

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** National Research Foundation (NRF) RS-2022-NR072217 of Korea Grant

**Title:** Molecular and Electrophysiological Diversity of Piezo2-Expressing Dental Primary Afferent Neurons

**Authors:** \*P. LEE<sup>1</sup>, K. LEE<sup>2</sup>, S. OH<sup>3,4</sup>;

<sup>1</sup>Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of; <sup>2</sup>Tooth-Periodontium Complex Med. Res. Ctr., Seoul Nat'l Univ., Seoul, Korea, Republic of; <sup>3</sup>Sch. of Dent. & Dent. Res. Inst., Seoul Nat'l Univ., Seoul, Korea, Republic of; <sup>4</sup>ADA Forsyth Inst., Cambridge, MA

**Abstract:** Piezo2, a key mechanosensitive ion channel, is broadly expressed in dental primary afferent (DPA) neurons and has been implicated in hypersensitivity to mild mechanical irritations, a common clinical feature of dental pain. To investigate the molecular and functional diversity of Piezo2-expressing DPA neurons, we employed immunohistochemistry, patch-clamp electrophysiology, single-cell RT-PCR, single-cell transcriptomic analysis, and fluorescence in situ hybridization (FISH). We identified two distinct action potential (AP) types based on waveform morphology, each associated with unique expression patterns of TRPV1 and tetrodotoxin-resistant sodium channels Nav1.8 and Nav1.9. Single-cell transcriptomic analysis further revealed that neuropeptides, including CGRP isoforms, Substance P, and Galanin, were differentially expressed across AP subtypes and correlated with Nav1.8/1.9 expression. These molecular associations were confirmed in Piezo2<sup>+</sup> DPA neurons using FISH. Together, our findings highlight the molecular and electrophysiological heterogeneity of Piezo2<sup>+</sup> DPA neurons and suggest their potential role in aberrant encoding of normally innocuous mechanical irritations.

**Disclosures:** P. Lee: None. K. Lee: None. S. Oh: None.

## Poster

### PSTR219: Headache, Migraine, and Trigeminal Circuits

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR219.29/L3

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH grant DC020843-01

**Title:** Role of TRPM8 ion channels in taste and learned oral thermal preferences

**Authors:** \*K. T. ZUMPARNO, C. H. LEMON;  
Sch. of Biol. Sci., Univ. of Oklahoma, Norman, OK

**Abstract:** The role of TRPM8 thermoreceptors in oral sensory preferences in rodents is beginning to be explored. Previous work from our lab has shown that TRPM8 ion channels discern cool from oral warm signaling in mice, as TRPM8 loss leads to generalization between innocuous cool and aversively warm temperatures. It is unclear how TRPM8 oral thermal signals

contribute to taste preferences. To study this, we explored how TRPM8 input is involved in learning about oral temperatures in ingestive behavior settings with mice deficient for this ion channel and C57BL/6J (B6) controls. In addition, we examined how TRPM8 input and loss affects taste preferences to sweet taste solutions. To study learning, we examined the ability of B6 and TRPM8<sup>-/-</sup> mice to generalize a conditioned preference (CP) between normally preferred ( $\leq 30^{\circ}\text{C}$ ) and avoided ( $\geq 30^{\circ}\text{C}$ ) warm oral temperatures, with preferences shown in prior work (Li et al. 2024). These tests used a custom lickometer that monitors mouse licking of temperature-controlled fluids during brief-access exposure tests. In one experiment, we hypothesized that TRPM8<sup>-/-</sup> mice will generalize a CP for mild cool/warm  $28^{\circ}\text{C}$  water (CS+) with water warmed to a novel warm temperature ( $33^{\circ}\text{C}$ ) while B6 mice will not. This was based on data showing TRPM8 involvement in discerning these oral temperatures ranges, as above. As hypothesized, results show that TRPM8<sup>-/-</sup> mice ( $n = 8$ ) generalized a CP to  $28^{\circ}\text{C}$  water with  $33^{\circ}\text{C}$  water as they were indifferent to lick the two stimuli (Friedman's ANOVA,  $p = 1$ ). In contrast, B6 mice did not generalize  $28^{\circ}\text{C}$  water with  $33^{\circ}\text{C}$  water and instead exhibited a "peak shift" like response, preferring  $33^{\circ}\text{C}$  over the CS+  $28^{\circ}\text{C}$  ( $p = 0.034$ ). Peak shift is an effect where a CP is enhanced to a stimulus of greater magnitude than the conditioned stimulus (Ahmed and Lovibond, 2019). A second experiment was done to study the effects of TRPM8 on taste preference for sucrose. Since mild cool/warmth increases neural responses to sucrose (Lemon, 2017), we hypothesized that B6 mice would prefer  $28^{\circ}\text{C}$  sugar solutions over cooled. In TRPM8<sup>-/-</sup> mice, we expected that  $28^{\circ}\text{C}$  sugar solutions would be avoided, agreeing with avoidance of water at similar temperatures in the absence of TRPM8, as above. Preliminary data show B6 mice ( $n = 4$ ) preferred to lick 1.0 M sucrose at  $28^{\circ}\text{C}$  over cool temperatures ( $10^{\circ}\text{C}$ ; Friedman's ANOVA,  $p = 0.0455$ ). In contrast, TRPM8<sup>-/-</sup> mice ( $n = 4$ ) did not increase licking of 1.0 M sucrose at  $28^{\circ}\text{C}$  compared to  $10^{\circ}\text{C}$  ( $p = 1$ ). Additional mice will be tested to build power. Together, these data demonstrate that TRPM8 input provides a sensory "boundary" between mild cool and warm temperatures and loss leads to generalizing licking avoidance of warmth to cooler temperatures.

**Disclosures:** K.T. Zumpano: None. C.H. Lemon: None.

## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.01/L4

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Cyclic fluctuations in pain sensitivity associated with the sex hormonal cycle in male cynomolgus monkeys

**Authors:** \*K. HAYASHIDA<sup>1</sup>, D. MORI<sup>1</sup>, Y. MITSUKURA<sup>2</sup>;

<sup>1</sup>Pharmacol., Shin Nippon Biomed. Laboratories, Ltd., Kagoshima, Japan; <sup>2</sup>Keio Univ., Kanagawa, Japan

**Abstract:** In females, fluctuations in pain sensitivity correlating with sex hormone cycles are well established. Although males also experience sex hormonal cycles and testosterone is known to exert analgesic effects, periodic changes in male pain sensitivity have not been reported. This study investigated whether pain sensitivity and serum testosterone levels are associated, and if they exhibit periodicity in adult male cynomolgus monkeys (6-8 years old,  $n = 8$ ), a non-seasonal breeding primate species similar to humans. Periodic changes in testicular volume were also examined. Pain sensitivity, measured by paw withdrawal temperature (PWT) in the dorsal hind paws, along with serum testosterone levels and testicular volume, showed periodic fluctuations. The average intervals ( $\pm$  SD) between peak values were  $20.1 \pm 4.7$  days for PWT,  $40.2 \pm 14.2$  days for testosterone levels, and  $51.5 \pm 14.2$  days for testicular volume. These cycles were not synchronized, however, the testosterone peak intervals significantly correlated with PWT ( $P < 0.001$ ) and testicular volume ( $P = 0.017$ ) peak intervals. Moreover, the testosterone peak amplitude significantly correlated with that of PWT ( $P = 0.037$ ), consistent with the analgesic effect of testosterone. These results demonstrate the presence of a male sexual cycle in cynomolgus monkeys, as evidenced by periodic changes in testosterone levels and testicular volume, along with cyclic fluctuations in thermal pain sensitivity that correlate with testosterone periodicity. This study provides new insights into the role of male hormone cycles in the regulation of pain, not only in cynomolgus monkeys but potentially in other non-seasonal breeding primates, including humans.

**Disclosures:** K. hayashida: None. D. Mori: None. Y. Mitsukura: None.

## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.02/L5

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NRF-2023R1A2C3002798  
RS-2023-00302281  
NRF-2021R1C1C2005440

**Title:** Spino-cerebral metabolic mapping after spinal nerve ligation: A longitudinal dual-region FDG-PET study

**Authors:** \*J. CHO, J.-Y. PARK, H.-I. KIM;  
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**Abstract:** Peripheral nerve injury induces widespread neuroplastic changes along both ascending and descending pain pathways. However, the temporal and spatial interplay between spinal and supraspinal regions during pain chronification remains poorly understood. In this study, we conducted longitudinal [ $^{18}\text{F}$ ]-FDG microPET imaging of the brain and spinal cord in male Sprague-Dawley rats subjected to spinal nerve ligation (SNL group,  $n = 10$ ) or sham surgery ( $n =$



9) on postoperative days 4, 14, and 28. To assess changes in glucose metabolism over time, PET images were analyzed using a group-level linear mixed-effects model (3dLME in AFNI). In addition, immunohistochemical analysis (Iba1 and GFAP) was conducted at each time point (n = 5/group) in the spinal cord. The SNL group showed increased glucose metabolism in the ipsilateral dorsal horn (L5), as well as in several pain-related brain regions along ascending and descending pathways. On postoperative day 4, a marked decrease in glucose metabolism was observed in the bilateral primary and secondary somatosensory cortices (S1/S2) and motor cortices (M1/M2). Notably, this cortical hypometabolism persisted through day 28, indicating a sustained suppression of pain processing in the cortex. From day 14 onward, progressive metabolic changes emerged in the bilateral insular cortices, the ipsilateral amygdala, the contralateral thalamus, hypothalamus, periaqueductal gray (PAG), and rostral ventromedial medulla (RVM), indicating the engagement of limbic and descending modulatory circuits. Immunohistochemical analysis revealed time-dependent activation of microglia and astrocytes in the spinal dorsal horn, mirroring the PET signal changes. These findings illustrate a spatiotemporal progression of pain-related neuroplasticity, delineating glia-driven hyperexcitability along ascending pathways and engagement of descending limbic-brainstem modulatory networks during pain chronification. Our dual-region longitudinal imaging characterizes the spino-cerebral metabolic trajectory of neuropathic pain. We identified a distinct pattern of persistent cortical hypometabolism and brainstem-limbic hyperactivity, underpinned by spinal gliosis. These findings provide a mechanistic rationale for motor cortex stimulation (MCS) as a potential intervention to restore cortical excitability and enhance descending inhibitory control in chronic pain.

**Disclosures:** J. Cho: None. J. Park: None. H. Kim: None.

## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.03/L6

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH - R21 NS118162  
University of Rochester Psychiatry Department

**Title:** Decision-making deficits and resting-state neural markers in temporomandibular joint disorder (TMD): linking pain to motivation

**Authors:** \*O. CARACCIO<sup>1</sup>, C. MAHLEN<sup>2</sup>, J. KHAN<sup>3</sup>, E. ELIAV<sup>4</sup>, P. GEHA<sup>1,2</sup>;  
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**Abstract:** Chronic pain is pervasive in the United States, affecting over 116 million Americans and costing up to \$635 billion annually in medical expenses, lost productivity, and disability

payments. Temporomandibular joint disorders (TMD) account for 5-12% of all chronic pain conditions and disproportionately affect younger adults and women. TMD is frequently comorbid with depression, anxiety, and stress, suggesting a central neural motivational component. However, its exact pathophysiology remains unclear. We aimed to test whether TMD shares behavioral and neural abnormalities identified in other chronic pain populations. Specifically, we seek to determine whether TMD patients exhibit behavioral deficits and brain changes indicative of plasticity within the motivational brain circuitry, which has been repeatedly implicated in other chronic pain disorders. We recruited 13 TMD patients and 13 pain-free healthy controls (HCs) that were matched for age (mean age = 31), sex (9 females), and BMI. TMD patients were identified by their dentist and reported pain for > 1 year. All participants completed 2 sessions which included computer-based surveys and behavioral tasks testing cognitive function and decision making: Iowa Gambling Task (IGT), Wisconsin Card Sorting Task (WCST), and Effort Expenditure for Reward Task (EEfRT). Participants completed 10 minutes of resting state functional magnetic resonance imaging (fMRI) to measure brain power spectral density and functional connectivity within the motivational system. Overall, TMD patients were less likely to learn from mistakes. In the IGT, TMD patients did not learn to avoid “risky” decks over the course of 100 trials compared to HCs. Similarly, the WCST showed that TMD patients did not learn to avoid perseveration errors, unlike HCs. The EEfRT task revealed TMD patients expended less effort than HCs especially when faced with low reward magnitude, but they recovered faster as the reward magnitude increased. Using a functional brain biomarker identified in patients with chronic low-back pain-loss of power spectral density in the slow-5 frequency band (0.01-0.027 Hz)-we can distinguish between TMD patients and HCs using a receiver operating characteristic curve, with an area under the curve of 0.71 ( $p = 0.048$ ). We did not identify any significant functional connectivity differences between the groups. Our preliminary analysis corroborates partly our hypothesis that TMD patients may share behavioral and neural changes indicative of disruptions in the motivational brain system, an observation validated in other chronic pain conditions.

**Disclosures:** O. Caraccio: None. C. Mahlen: None. J. Khan: None. E. Eliav: None. P. Geha: None.

## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.04/L7

**Topic:** E.01. Somatosensation – Pain and Itch

**Title:** Robust decoding of post-operative pain and analgesic states from iEEG recordings

**Authors:** \*Y. ZHAO<sup>1</sup>, R. PEREZ<sup>5</sup>, B. SEIDENBERG<sup>5</sup>, A. SEEDAT<sup>5</sup>, G. KENEFATI<sup>5</sup>, M. ROCKHOLT<sup>5</sup>, H. MARTINEZ<sup>5</sup>, G. SOTO-ARZON<sup>5</sup>, Q. ZHANG<sup>6</sup>, L. YU<sup>5</sup>, F. ZHOU<sup>2</sup>, X. LIU<sup>3</sup>, A. FLINKER<sup>4</sup>, L. DOAN<sup>5</sup>, E. OERMANN<sup>5</sup>, D. FRIEDMAN<sup>5</sup>, J. WANG<sup>6</sup>;

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<sup>4</sup>Neurol., New York Univ., New York, NY; <sup>6</sup>Anesthesiol., <sup>5</sup>NYU Grossman Sch. of Med., New York, NY

**Abstract:** Post-operative pain significantly impacts patient recovery, underscoring the need for precise and effective pain management. However, clinicians rely primarily on subjective self-reporting for pain assessment and treatment, while objective biomarkers for pain evaluation remain underdeveloped. In this study, we applied machine learning models to decode post-operative pain and analgesic states using intracranial EEG (iEEG) recordings from epilepsy patients implanted with electrodes in the anterior cingulate cortex (ACC) and insula. Patients received standard post-operative analgesics and reported their pain levels on a 0-10 numeric rating scale. Episodic iEEG recordings were collected before and after analgesic administration over a span of 6 to 21 days. Power features from multiple frequency bands(delta: 1-4 Hz, theta: 4-8 Hz, alpha: 8-12 Hz, beta: 12-30 Hz, gamma: 30-57 Hz, high-gamma: 63-100 Hz, and multi-unit activity: 100-300 Hz) were extracted and used to train support vector machine (SVM) and linear discriminant analysis (LDA) classifiers. Five-fold cross-validation demonstrated that the SVM model could accurately predict both pain and analgesic states, achieving ROC-AUC of  $0.97 \pm 0.028$ . Importantly, trained models generalized well to subsequent days, with ROC-AUCs of  $0.84 \pm 0.074$ , indicating robust temporal stability. Decoder outputs aligned closely with the timing and type of administered analgesics. These findings position intracranial EEG recordings from ACC and insula as a promising source of objective neural biomarkers for pain and analgesic monitoring, potentially enabling closed-loop neuromodulation and demand-based pain management.

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## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.05/Web Only

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** R01HD096332

**Title:** Longitudinal EEG changes across menarche reveal early neurophysiological markers of menstrual pain risk

**Authors:** \***N. R. OSBORNE**<sup>1,2</sup>, F. F. TU<sup>1,2</sup>, S. E. DARNELL<sup>1</sup>, K. M. HELLMAN<sup>1,2</sup>;

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**Abstract:** Menarche - the first menstruation - occurs during a key neurodevelopmental period in adolescence. Both earlier age at menarche and painful periods (i.e., dysmenorrhea) in adulthood are associated with an increased risk for chronic pain. However, few studies have specifically investigated how the brain changes over the menarchal transition and how these changes may relate to subsequent menstrual pain. Here we used longitudinal resting-state 64-channel electroencephalography (EEG) to characterize functional brain organization in 197 adolescents before and after menarche. EEG data was preprocessed and analyzed using the DiscoverEEG pipeline. We found extensive changes in brain oscillations between the pre-menarche visit (n=185, age = 11 (10,12) years), the first post-menarche visit (n= 163, age = 13 (12, 14) years) and the second post-menarche visit (n=132, age = 14 (14, 15) years). These included decreases in global theta power ( $p < 0.025$ ) and increases in peak alpha frequency (PAF,  $BF_{10}=211.12$ ,  $p<0.001$ ). We also found decreases in theta and alpha functional connectivity after menarche ( $BF_{10} > 30$ ), which may reflect synaptic pruning. While increases in alpha and beta power are typically reported with increasing age in adolescence, we found decreased global alpha and beta power from the pre-menarche to the first post-menarche visit. Subsequent segregated analyses of adolescents with dysmenorrhea (menstrual pain rating  $> 30/100$  on a visual analogue scale) versus controls found global alpha and beta power decreases in dysmenorrhea only ( $p < 0.025$ ). We also found dysmenorrhea-specific alterations in PAF at multiple time points. Adolescents with dysmenorrhea had a higher PAF ( $BF_{10}=1.40$ ,  $p < 0.05$ ) compared to controls at the first post-menarche visit, and did not show the longitudinal increase in PAF from the first to second post-menarche visit that was seen in controls. Interestingly, a higher peak alpha frequency ( $BF_{10}=1.22$ ,  $p < 0.05$ ) was also observed at the pre-menarche visit in adolescents who would later go on to develop dysmenorrhea. This suggests that there may be brain mechanisms that predispose individuals to greater menstrual pain. Overall, our findings agree with prior literature showing that in adolescence EEG oscillations shift toward faster frequencies, low-frequency connectivity decreases, and network efficiency increases—hallmarks of synaptic pruning and neuroplastic reorganization. Deviations from this trajectory, such as lower alpha/beta power and higher PAF in those with menstrual pain, may indicate altered sensory integration or brain maturation and provide a potential window into early identification of pain risk.

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## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.06/L8

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH R15 NS137286-01A1

**Title:** Alpha (8-13 Hz) EEG activity during the cognitive processing of sensory and affective pain descriptor words

**Authors:** \*S. LOVE<sup>1</sup>, A. RONCK<sup>1</sup>, B. BALLENGER<sup>1</sup>, K. MALAVAR<sup>1</sup>, L. ROWDEN<sup>1</sup>, A. NORRIS<sup>1</sup>, M. WIRTZ<sup>1</sup>, A. PARK<sup>2</sup>, A. L. HARRIS BOZER<sup>1</sup>;

<sup>1</sup>Tarleton State Univ., Stephenville, TX; <sup>2</sup>Univ. of Central Arkansas, Conway, AR

**Abstract:** Pain is multidimensional and significantly impacts cognitive functioning, yet the EEG activity underlying the cognitive processing of the sensory-discriminative and affective-motivational dimensions of pain remains insufficiently investigated. The aim of this study was to evaluate alpha band (8-13 Hz) EEG activity from the somatosensory cortices (C3 & C4), the thalamus (F7), and anterior cingulate and insula (F8) during the presentation of sensory and affective pain descriptor words with an acute pain condition (cold pressor). Pain descriptor words consisted of validated sensory and affective words derived from the Short Form McGill Pain Questionnaire, and required a participant's response. EEG data were recorded (Magstim EGI; 256 electrodes) for 20 participants (11 females) and processed in Net Station. One-way repeated measures ANOVAs were computed for the processed alpha EEG data at each electrode during the six time-based EEG recordings: (1) baseline resting state, (2) sensory words, (3) affective words, (4) cold pressor, (5) cold pressor with sensory words, and (6) cold pressor with affective words. Within-subjects tests revealed a main effect of time at all four electrodes (C3, C4, F7, F8; all  $p < .001$ ). Bonferroni pairwise comparisons revealed that cold pressor pain alone did not significantly increase activity in any electrodes of interest. In contrast, viewing sensory pain descriptor words did significantly increase alpha activity at all electrodes (C3, C4, F7, F8), and during cold pressor pain at F7 and F8. Further, there was significantly greater alpha during affective words compared to sensory words at C3, C4, and F7, and during cold pressor at electrodes F7 and F8. In the current study, cold pressor pain alone did not increase activity in electrodes associated with the thalamus, primary somatosensory, anterior cingulate, and insular cortices. However, when pain descriptor words were presented, requiring the participant to cognitively process aspects of their pain, alpha oscillations significantly increased. These data indicate that alpha oscillations are generated not just by the presence of pain, but by the cognitive processing of pain. These findings contribute to our knowledge of cortical activities that underlie the cognitive processing of the multidimensional nature of pain.

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**Poster**

**PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.07/L9

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH R15 NS137286-01A1

**Title:** Theta (31-50Hz) band EEG during the cognitive processing of multidimensional pain descriptor words

**Authors:** \*A. RONCK<sup>1</sup>, B. BALLENGER<sup>1</sup>, S. LOVE<sup>1</sup>, K. MALAVAR<sup>1</sup>, L. ROWDEN<sup>1</sup>, A. NORRIS<sup>1</sup>, M. WIRTZ<sup>1</sup>, A. PARK<sup>2</sup>, A. L. HARRIS BOZER<sup>1</sup>;

<sup>1</sup>Tarleton State Univ., Stephenville, TX; <sup>2</sup>Univ. of Central Arkansas, Conway, AR

**Abstract:** Pain is multidimensional and has sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions. While neural mechanisms that support the processing of pain have been extensively investigated, the EEG cortical activity that is linked to cognitive processing of pain, specifically within the sensory and affective dimensions, is under-explored. The aim of this study was to assess theta (4-7 Hz) EEG activity originating from the C3 and C4 (somatosensory cortices), the F7 (thalamus), and F8 (anterior cingulate and insula) electrodes during the delivery of sensory and affective pain descriptor words and acute pain induced by a cold pressor. EEG data were collected (Magstim EGI; 256 electrodes) from each participant (N=20; 11 females) during four time bins: resting state EEG, during presentation of sensory and affective pain descriptor words, cold pressor pain with resting state EEG, and cold pressor pain with sensory and affective words. Pain descriptor words were taken from the validated Short Form McGill Pain Questionnaire and included sensory and affective words. One-way repeated measures ANOVAs were computed for theta EEG activity for each electrode of interest (C3, C4, F7, F8), and each time bin with sensory and affective treated as separate conditions, resulting in six distinct bins: (1) baseline resting state, (2) sensory pain descriptor words, (3) affective pain descriptor words, (4) cold pressor, (5) cold pressor with sensory words, and (6) cold pressor with affective words. Within-subjects tests revealed a main effect of time for theta activity for all four electrodes (C3, C4, F7, F8) (all  $p < .001$ ). Bonferroni comparisons revealed that cold pressor pain alone did not elicit a significant increase in activity in any electrode ( $p > .05$ ). In contrast, there was a significant increase in theta while processing sensory and affective pain descriptor words during the presentation of affective words with cold pressor pain at all electrodes, and during the presentation of sensory pain descriptors at C4 and F8 during cold pressor pain ( $p < .05$ ). Affective words elicited higher theta activity than sensory words, with greater averages across all electrodes, including C3 and C4, typically associated with sensory processing. These findings expand the knowledge of theta band EEG activity in the processing of sensory and affective pain and can contribute to creating an in-depth understanding of the EEG cortical activity that underlies pain.

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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 R15 NS137286-01A1. **A.L. Harris Bozer:** 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 R15 NS137286-01A1.

## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.08/L10

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH R15NS137286-01A1

**Title:** Investigating gamma (31-50Hz) band EEG activity in response to cognitive processing of sensory and affective pain descriptor words

**Authors:** \***B. BALLENGER**<sup>1</sup>, K. MALAVAR<sup>2</sup>, S. LOVE<sup>2</sup>, A. RONCK<sup>2</sup>, L. ROWDEN<sup>2</sup>, A. NORRIS<sup>2</sup>, M. WIRTZ<sup>2</sup>, A. PARK<sup>3</sup>, A. L. HARRIS BOZER<sup>2</sup>;

<sup>1</sup>Tarleton State Univ., dublin, TX; <sup>2</sup>Tarleton State Univ., Stephenville, TX; <sup>3</sup>Univ. of Central Arkansas, Conway, AR

**Abstract:** Pain is multidimensional and profoundly impacts cognitive processing, yet the EEG activity that underlies the cognitive processing of the sensory and emotional dimensions of pain remains poorly understood. Gamma brainwaves are associated with focus, concentration, and awareness and have been implicated in previous pain research. The current study aimed to elucidate the role of gamma band oscillations in the cognitive processing of the multidimensional nature of pain. We investigated gamma (31-50 Hz) EEG activity from the thalamus (F7), anterior cingulate and insula (F8) and somatosensory cortices (C3 & C4), while 20 participants (11 females) responded to pain descriptor words (sensory and affective) taken from the validated Short Form McGill Pain Questionnaire. Six time-based EEG recordings (Magstim EGI; 256 electrodes) were recorded: (1) a resting state baseline, (2) during the presentation of sensory pain descriptor words, (3) during the presentation of affective pain descriptor words, (4) during a cold pressor acute pain stimulus, (5) cold pressor with sensory words, and (6) cold pressor with affective words. One-way repeated measures ANOVAs run with gamma EEG activity over time indicated a main effect of time at three electrodes (C3, F7, and F8;  $p < .05$ ). Bonferroni pairwise comparisons revealed that cold pressor pain did not significantly increase gamma activity over baseline at any of these electrodes ( $p > .05$ ). At the C3 electrode, presentation of sensory and affective pain descriptor words significantly increased gamma activity over baseline, as well as sensory and affective words during the acute cold pressor pain stimulus, ( $p < .05$ ). At F8, only sensory and affective words during cold pressor stimuli significantly increased gamma over baseline ( $p < .05$ ). Gamma showed the highest activity when accompanied by both the pain descriptor words with the cold pressor stimuli in electrodes receiving input from the thalamus

and somatosensory cortex, demonstrating the role of gamma frequency activities in these areas in the cognitive processing of pain over and above the pain itself. Taken together, these data contribute to the understanding of the role of gamma in the cognitive processing of multidimensional pain stimuli.

**Disclosures:** **B. Ballenger:** A. Employment/Salary (full or part-time): NIH R15 NS137286-01A1. **K. Malavar:** A. Employment/Salary (full or part-time): NIH R15 NS137286-01A1. **S. Love:** A. Employment/Salary (full or part-time): NIH R15 NS137286-01A1. **A. Ronck:** None. **L. Rowden:** None. **A. Norris:** None. **M. Wirtz:** None. **A. Park:** 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 R15 NS137286-01A1. **A.L. Harris Bozer:** 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 R15 NS137286-01A1.

## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.09/L11

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH R15 NS137286-01A1

**Title:** Alpha (8-13 Hz) EEG and electrodermal responses to multidimensional pain descriptors and cold pressor pain

**Authors:** L. ROWDEN<sup>1</sup>, A. NORRIS<sup>1</sup>, M. WIRTZ<sup>1</sup>, S. LOVE<sup>1</sup>, B. BALLENGER<sup>1</sup>, K. MALAVAR<sup>1</sup>, A. RONCK<sup>1</sup>, A. PARK<sup>2</sup>, \*A. L. HARRIS BOZER<sup>1</sup>;

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**Abstract:** Cortical activities in the alpha frequencies (8-13 Hz) have been extensively associated with pain. However, the relationship between the peripheral sympathetically elicited response and cortical activity in the alpha band during the cognitive processing of the multidimensional nature of pain has not been fully elucidated. Participants (N=20; 11 females) underwent simultaneous EEG recordings (Magstim EGI; 256 electrodes) and electrodermal recordings (Neulog GSR) at four time points: baseline- resting state, during the presentation of sensory and affective pain descriptor words taken from the validated Short-Form McGill Pain Questionnaire, during an acute pain stimulus induced by cold pressor, and application of the cold pressor stimulus during the presentation of the pain descriptor words. The electrodes of interest for the current study were previously associated with pain and purportedly receive input from the somatosensory cortices (C3 and C4), thalamus (F7), anterior cingulate and insular cortices (F8). Pearson's correlations were computed to examine the potential relationship between



electrodermal activity and alpha frequency EEG activity at each time bin. The results revealed the significant correlations between alpha EEG activity and electrodermal activity occurring during 1) the presentation of sensory and affective pain descriptor words at the C3 electrode ( $r=0.470$ ,  $p=0.037$ ) and 2) the acute pain stimulus by cold pressor at the F7 electrode ( $r=0.525$ ,  $p=0.017$ ). These data indicate the relationship of the electrodermal response with the somatosensory cortex in processing multidimensional pain stimuli and the thalamus and electrodermal response during acute pain. Future research will examine the relationship between electrodermal activity and alpha cortical activity in a sample with chronic knee osteoarthritis and examine any potential for differential response to sensory and affective pain descriptor words. This research will contribute to the body of literature that aims to evaluate the electrodermal response as an ancillary measure of the response to pain.

**Disclosures:** **L. Rowden:** None. **A. Norris:** None. **M. Wirtz:** None. **S. Love:** None. **B. Ballenger:** A. Employment/Salary (full or part-time): NIH R15 NS137286-01A1. **K. Malavar:** A. Employment/Salary (full or part-time): NIH R15 NS137286-01A1. **A. Ronck:** None. **A. Park:** 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 R15 NS137286-01A1. **A.L. Harris Bozer:** 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 R15 NS137286-01A1.

## **Poster**

### **PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR220.10/L12

**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH Grant K08DA037525

**Title:** Functional MRI reveals changes in brain response to a highly-palatable drink in chronic pain patients

**Authors:** \***C. MAHLEN**<sup>1</sup>, H. MREYDEM<sup>1</sup>, I. E. DE ARAUJO<sup>2</sup>, D. M. SMALL<sup>3</sup>, P. Y. GEHA<sup>4</sup>;

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**Abstract:** Chronic pain and obesity are interrelated. Chronic pain patients are at increased risk of overeating and obesity, and obese subjects are more likely to develop chronic pain. To date, the mechanism of this association is still unknown. While some investigators suggested that fear of

pain exacerbation leads patients to a more sedentary lifestyle and, as a result, burn less calories, objective measures of physical activity in chronic pain patients show they are as active as the general population.

In this study we set out to test a novel hypothesis that chronic pain patients exhibit a different neural response to highly palatable foods when not hungry, which would put them at risk of overeating. The hypothesis stems from accumulating evidence showing that the corticostriatal pathways governing feeding related decisions, are altered in pain patients and play a critical role in tracking and predicting clinical pain.

We presented 28 chronic low-back pain (CLBP, pain duration > 1 year, pain > 30/100 on the visual analog scale) patients and 31 healthy controls matched for age, sex, BMI, education, and physical activity with highly palatable milkshakes while recording their brain activity via fMRI. We controlled for somatosensory responses by using tasteless stimuli as controls and for swallowing-related activity by tracking swallowing events and ensured that both groups were neither hungry nor full prior to the brain scan. We hypothesized that CLBP patients would show altered brain responses to milkshakes in three limbic regions: the amygdala, nucleus accumbens, and the ventromedial prefrontal cortex.

Results revealed no significant differences in hemodynamic responses within any of the hypothesized limbic regions. However, a whole-brain analysis identified altered hemodynamic responses in the bilateral motor cortices, right insula, right angular gyrus, and right frontal operculum ( $q < 0.05$ , FDR whole brain corrected). Additionally, the responses in the motor cortices and operculum significantly correlated with CLBP patients' pain ratings.

Although our initial hypothesis—that CLBP patients would exhibit altered hedonic responses to a highly palatable milkshake in canonical reward-related limbic regions—was not supported, our findings reveal an unexpected pattern that contributes to a shifting understanding of how chronic pain affects the brain's response to food-related stimuli. The observed differences in motor cortices and right frontal operculum suggest that motor and sensorimotor networks may play a previously underappreciated role in modulating the experience of reward in chronic pain.

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## **Poster**

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**Title:** Insights from hyperscanning: synchronized dual-brain fMRI to investigate longitudinal mechanisms of patient-clinician dyadic interactions

**Authors:** \*A. GRAHL<sup>1</sup>, A. ANZOLIN<sup>1</sup>, L. GARDINER<sup>1</sup>, S. ELLIS<sup>1</sup>, J. LEE<sup>1</sup>, C. JUNG<sup>2</sup>, M. BARTON-ZUCKERMAN<sup>3</sup>, K. ISENBURG<sup>1</sup>, D.-M. ELLINGSEN<sup>4</sup>, T. DOAN<sup>1</sup>, I. HEWARDT<sup>1</sup>, S. LEE<sup>1</sup>, R. EDWARDS<sup>5</sup>, J. KELLEY<sup>6</sup>, T. J. KAPTCHUK<sup>7</sup>, V. NAPADOW<sup>1</sup>;

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**Abstract:** The nature of clinical interactions plays a pivotal role in establishing patient trust and fostering a strong therapeutic alliance. Our prior fMRI hyperscanning work showed that brain concordance between patients and clinicians - especially in the temporoparietal junction (TPJ) - was associated with analgesia in individuals with fibromyalgia (Ellingsen et al., 2020).

Additionally, warm, empathic clinician styles (Augmented) have been linked to better treatment outcomes than neutral, business-like (Limited) approaches. This longitudinal study explores how different clinician interaction styles influence chronic pain patients' brain responses and how these neural patterns relate to the development of therapeutic alliance over time. Thirty-two women with fibromyalgia (FM, mean age=38.5±12.7 years) were randomly assigned to an Augmented (N=17) or Limited (N=15) patient-clinician dyadic interaction style (trained acupuncturists). Each dyad underwent synchronized real-time dual-brain fMRI with a real-time video connection between two 3T MRI scanners and an evoked cuff pressure pain/treatment paradigm (TR/TE=1250/33ms; SMS MB acc. factor 5; voxel size 2mm<sup>3</sup>; 2x358 volumes) before and after 3-weeks of acupuncture (6 treatment sessions). The quality of the patient-clinician relationship and clinical outcomes were assessed via self-report questionnaires. Patients rated therapeutic alliance, clinicians' warmth, competence, and level of trust significantly higher in the Augmented group ( $t_{\text{alliance}}(30)=5.87$ ,  $p<0.001$ ;  $t_{\text{warmth}}(30)=6.27$ ,  $p<0.001$ ;  $t_{\text{comp}}(30)=3.09$ ,  $p=0.004$ ;  $t_{\text{trust}}(30)=6.15$ ,  $p<0.001$ ). While both groups experienced fibromyalgia pain relief after acupuncture ( $p<0.001$ ), the Augmented group reported significant greater reduction in pain catastrophizing ( $F(1,30)=9.37$ ,  $p=0.005$ ). Following acupuncture, patients' fMRI response to evoked pressure pain in nociceptive processing areas (i.e. S2, posterior insula, SPL) was reduced. Brain-to-brain concordance analyses focused on the social mirroring circuitry to understand the neural mechanisms underlying inter-dyad differences in the quality of the therapeutic alliance. Our findings indicate that more supportive clinical interactions may enhance salience-related brain processing, possibly reflecting deeper engagement between patient and clinician during pain treatment. This study underscores the critical role of the therapeutic relationship in shaping outcomes for chronic pain patients and identifies potential neural mechanisms that may mediate these effects.

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**Poster**

**PSTR220: Pain Imaging and Perception**

**Location:** SDCC Halls B-H

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**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** European Research Council (Advanced Grant SELF-UNITY, #787386)  
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**Title:** Feeling pain from a rubber hand: nociceptive drift in the rubber hand illusion

**Authors:** \*S. COPPI<sup>1</sup>, H. EHRSSON<sup>2</sup>;

<sup>1</sup>Karolinska Institutet, Solna, Sweden; <sup>2</sup>Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden

**Abstract:** The sense that our body belongs to ourselves is referred to as ‘*body ownership*’, and it is thought to emerge from multisensory integration mechanisms. To study this phenomenon, a widely used paradigm is the Rubber Hand Illusion (RHI): synchronous touches are applied to a rubber hand placed in view and to the participant’s own hand hidden behind a screen. The spatially and temporally congruent application of tactile stroking with coherent visual and proprioceptive inputs elicits the perceptual experience of owning the rubber hand in view. Recent research suggests that congruence between Aδ and C fiber nociceptive signals and visual and proprioceptive inputs can also induce the illusory ownership of a rubber hand (the nociceptive RHI, ‘N-RHI’). In a series of 3 independent experiments (each featuring 30 naïve subjects,  $N_{\text{tot}} = 90$ ), the current study aimed firstly to compare the classical tactile RHI and the N-RHI to investigate their similarities and differences via the ownership questionnaire (experiment 1) and the proprioceptive drift task (experiment 2). The second aim of the study was to investigate whether multisensory integration underlying body ownership could influence the perceived location of a painful stimulus through a new task: the ‘*nociceptive drift*’ task (experiment 3). In each experiment, we included two experimental conditions (congruent visuo-nociceptive -  $VN_{\text{con}}$ , and congruent visuo-tactile -  $VT_{\text{con}}$ ) and two control conditions (incongruent visuo-nociceptive -  $VN_{\text{inc}}$ , and incongruent visuo-tactile -  $VT_{\text{inc}}$ ). The findings show that both RHIs were elicited by similar multisensory integration mechanisms and resulted in comparable levels of ownership over the rubber hand. The illusory quantification of the RHI ( $VN_{\text{con}}$  minus  $VN_{\text{inc}}$  vs.  $VT_{\text{con}}$  minus  $VT_{\text{inc}}$ ) did not differ significantly between the two versions of the illusion, in neither the questionnaire nor in the proprioceptive drift task. Finally, the second key finding shows that under the congruent conditions of both RHI paradigms, participants statistically significantly updated the localization of the painful stimulus closer to the rubber hand as compared to the respective control conditions. In conclusion, these results are important because they reveal that different pairs of sensory inputs (vision with touch or nociception) engage similar multisensory integration mechanisms underlying body ownership. Furthermore, they suggest that nociceptive signals are integrated according to the same principles as tactile and proprioceptive inputs, and uncover the multisensory nature of pain localization.

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## **Poster**

### **PSTR220: Pain Imaging and Perception**

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**Topic:** E.01. Somatosensation – Pain and Itch

**Support:** NIH Grant F30AT013174-01

**Title:** Investigation of Intensity-Dependent Behavioral, Neural, And Autonomic Interactions During Tonic Pain

**Authors:** \*A. STROHMAN, W. LEGON;  
Fralin Biomed. Res. Inst., Roanoke, VA

**Abstract:** INTRODUCTION: Pain involves a complex interplay between neural and autonomic activity during the anticipation, duration, and recovery periods of noxious stimuli, yet few studies have comprehensively investigated how these signals interact in these timeframes to produce the pain experience.

METHODS: In an ongoing study, healthy subjects (N=68) underwent a cold pressor test (CPT) to their left foot while recording 32-channel electroencephalogram (EEG), electrocardiogram, electrodermal activity, respiration, and continuous blood pressure. The CPT was performed at three stimulus intensities: room temperature (20-22 C), cold (10-12 C), and very cold (0-2 C). After a 1-minute anticipation period, subjects submerged their foot for a 2-minute CPT followed by a 2-minute recovery while continuously rating their pain intensity on a 0-10 sliding scale ranging from “no pain” to “worst pain imaginable.” 1-way repeated measures analysis of variance (rmANOVA) tested for significant differences between CPT trials during foot submersion across EEG power bands from 1-100 Hz, heart rate (HR), systolic blood pressure (SBP), respiration, tonic electrodermal activity (EDA), and phasic electrodermal responses (EDR).

RESULTS: The first 39 subjects (21F/18M) demonstrated mean +/- standard deviation (std) pain ratings for room temperature, cold, and very cold trials of 0.48 +/- 0.91, 3.43 +/- 2.55, and 6.78 +/- 2.55, respectively. After family-wise error rate correction, rmANOVA demonstrated significant differences in pain ratings ( $F(2,76) = 161.36$ ,  $p_{\text{corrected}} < 0.0001$ ), frontoparietal low gamma (31-60 Hz,  $F(2,76) = 5.93$ ,  $p_{\text{corrected}} = 0.049$ ) and high gamma (61-100 Hz,  $F(2,76) = 6.37$ ,  $p_{\text{corrected}} = 0.033$ ) EEG powers, tonic EDA ( $F(2,76) = 15.67$ ,  $p_{\text{corrected}} < 0.0001$ ), HR ( $F(2,76) = 37.91$ ,  $p_{\text{corrected}} < 0.0001$ ), and SBP ( $F(2,76) = 12.42$ ,  $p_{\text{corrected}} = 0.0003$ ). Post hoc testing revealed each measure significantly increased with increasing CPT stimulus intensity. High gamma power significantly correlated with systolic blood pressure ( $r = 0.33$ ,  $p = 0.041$ ) but not heart rate ( $r = 0.14$ ,  $p = 0.40$ ) or tonic EDA ( $r = 0.003$ ,  $p = 0.98$ ) during the high intensity CPT trial.

DISCUSSION: The CPT produces intensity-dependent behavioral, EEG, and autonomic responses with significant relationships between EEG gamma power and systolic blood pressure. Next steps include continued recruitment and in-depth analysis of EEG-autonomic interactions during each CPT stage (anticipation, stimulus, recovery).

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**Poster**

**PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR221.01/M1

**Topic:** E.03. The Chemical Senses

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**Title:** Effects of day/light cycles on olfactory acuity and behavior

**Authors:** \*R. NG<sup>1</sup>, C.-Y. SU<sup>3</sup>, Y. XIAO<sup>1,4</sup>, M. BELLAH<sup>2</sup>;  
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**Abstract:** Day/night cycles profoundly impact animals' physiology and behavior to allow adaptation to rhythmic environmental cues. Daily rhythmic behaviors are believed to be patterned by central clock neurons. However, it is unclear whether and how day/night cycles affect the sensory acuity of peripheral oscillators—including sensory neurons—to then drive rhythmic behaviors. This study identifies courtship as an odor-guided behavior that is regulated by circadian clocks, and uncovers how *Drosophila melanogaster* courtship-promoting Or47b neurons exhibit olfactory acuity which fluctuates rhythmically by day/night cycles. Mechanistically, day/night conditions are communicated through the antagonistic actions of two biogenic amines. Specifically, serotonin and octopamine can up- or down-regulate the expression of a cation channel subunit to dynamically regulate Or47b neuronal excitability, thereby allowing day/night cycles to rhythmically fine-tune pheromone acuity. As a result, male flies are more sensitive to aphrodisiac pheromone cues at night and therefore more motivated to court females. This striking phenotype demonstrates a critical role of the peripheral sensory oscillator in gating a rhythmic social behavior.

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**Poster**

**PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.02/M2

**Topic:** E.03. The Chemical Senses

**Title:** Neural computing of local interneurons in *Drosophila* larval antennal lobe

**Authors:** \*R. YANG<sup>1,2,3</sup>, G. SI<sup>3,2</sup>;

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**Abstract:** Normalization is a canonical neural computation in sensory and many other neural systems. In such a circuit, the magnitude of an output signal is within a certain range, regardless the magnitudes of input signals. In olfactory perception, local interneurons normalize odor-evoked responses across glomeruli to facilitate concentration invariant odor perception, so that enable odorant recognition and discrimination regardless of concentration. In previous studies, the overall properties of *Drosophila* olfactory glomerulus interneurons were described as input-dependent lateral inhibition, and the input-dependent normalization model was quantified. We use *Drosophila* larva's first olfactory center which is antennal lobe to probe this question. This relatively simple system uses only more than ten neurons to perform normalization computation. Benefiting from the advantage of using 'primary' odors in fly larva, we manipulate each input neuron individually to precisely stimulate interneurons. Using a combination of microfluidics, calcium imaging, and genetic techniques, we characterized the response profiles of individual interneurons to odor stimuli to determine their roles in normalization. We confirmed the presence of normalization in a larva, consistent with that in an adult fruit fly. We discovered that the response profile of different output neurons are different, indicating the normalization coding strategy for different output neurons is heterogeneous. Specifically, we identified a set of five pan-glomerular GABAergic interneurons(broad LNs) that are crucial to normalization. They exhibit unique response characteristics along two orthogonal dimensions: strength, and combinations of inputs. These neurons cover different intensity ranges, and their preferred input combinations are related to the properties of the inner attribute of the olfactory receptor neurons. Overall, these diverse interneurons cover the feature space of the input, suppressing outputs that carry different information. It significantly increases our understanding of olfactory processing in the antennal lobe.

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**Poster**

**PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.03/M3

**Topic:** E.03. The Chemical Senses

**Support:** NIH Grant K99DC021506

**Title:** The organization of the antennal lobe in the clonal raider ant

**Authors: \*D. D. FRANK;**  
Rockefeller Univ., New York, NY

**Abstract:** Ants are the invertebrate paragons of communication. Ants encode information as large arrays of pheromones which are released dynamically in response to the appropriate stimuli. These chemical messages are received and decoded by a highly complex olfactory system. Peripheral olfactory sensory neurons (OSNs) in the antennae are necessary for pheromone perception and the production of normal social behaviors in ants. However, despite interest in understanding ant behavior and sociality more broadly, researchers have largely been unable to ‘look under the hood’ to understand how social cues are processed by the ant nervous system. Here, I use transgenic clonal raider ants (*Ooceraea biroi*) to shine light on how olfactory system organization is adapted as a key processing center for communication in this organism. OSNs tuning is defined by the expression of molecular olfactory receptor ion channels (ORs), a family of genes which is massively expanded in ants. These cells project axons to a central olfactory processing area called the antennal lobe (AL) where they coalesce into globular structures called olfactory glomeruli and form a topographic map for the representation of the chemosensory environment. With approximately 500 olfactory glomeruli and a corresponding ~500 molecular ORs, the clonal raider ant AL is more complex than many other insects and is even evocative of the olfactory bulb in the brain of mammals. In fact, prior work in our lab suggests the evolution of sociality may have coincided with unique neurodevelopmental logic in the ant antennal lobe and that, surprisingly, its similarity to the mammalian olfactory bulb may also encompass developmental mechanisms. For example, ORs play a critical developmental role in the mouse and the ant, but are expendable in the fruit fly. This, and several other observations, have led to a hypothesis that spontaneous neuronal activity in early development may be important for patterning the ant AL - like the mouse olfactory bulb. However, it is neither known if ant OSNs exhibit spontaneous activity through development, nor if the structure of the AL is dependent upon it. Here, I test this hypothesis using *in vivo* GCaMP imaging, novel transgenic clonal raider ants which manipulate early OSN activity, and fluorescence microscopy.

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## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.04/M4

**Topic:** E.03. The Chemical Senses

**Title:** Critical cues are never suppressed: hierarchical regulation at the olfactory periphery of larval *Drosophila*

**Authors: \*C. YE<sup>1,2,3</sup>, G. SI<sup>3,2</sup>;**

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**Abstract:** Olfactory receptor neuron's (ORN) responses to odorants are largely determined by the olfactory receptor expressed. However, other factors besides the receptor type also contribute to the odorant-ORN responses. In *Drosophila* larvae, we observed that the activation of one ORN could inhibit other ORN's activity. Using a microfluidic setup with a set of primary odorants, each of which only activates a specific type of ORNs, we characterized the lateral inhibition among larval ORNs. We found that lateral inhibition could happen between ORNs, both within and across the dendritic bundles. However, this phenomenon varies across individuals and ORN pairs. After a systematic survey of eight-by-eight ORN pairs, we found that each ORN has a similar probability of inhibiting other ORNs on average. But in the case of being inhibited by other ORNs, certain ORNs are significantly different from others. Notably, Or49a, a receptor critical for mediating the avoidance behavior of larvae towards parasitic wasps, is rarely to be inhibited by other ORNs, and this property becomes more stable with development. This result indicates at the olfactory periphery level, a hierarchical regulatory relationship is already established, which could help prioritize critical olfactory cues to be sent to the brain. Characterizing the lateral inhibition among larval ORNs could deepen our understanding of modifying the olfactory code in the natural environment.

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## **Poster**

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**Title:** Morphological specialization of mosquito CO<sub>2</sub>-sensing olfactory receptor neurons

**Authors:** \*K. CAUWENBERGHS<sup>1</sup>, R. NG<sup>2</sup>, K.-Y. KIM<sup>5</sup>, M. ELLISMAN<sup>6</sup>, C.-Y. SU<sup>7</sup>, J. A. CHOY<sup>3</sup>, P. VIJAYAKUMAR<sup>4</sup>;

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**Abstract:** Hematophagous mosquitoes use carbon dioxide (CO<sub>2</sub>) as a key arousal signal that gates behavioral responses to host-derived cues. In *Ae. aegypti*, CO<sub>2</sub> is detected by olfactory receptor neurons (ORNs) in the sensory hairs (sensilla) on the maxillary palp. While the molecular mechanism and behavioral significance of CO<sub>2</sub> sensing have been well studied in mosquitoes, the nanoscale structure of their CO<sub>2</sub> ORNs has remained unclear. Here, we used serial block-face scanning electron microscopy (SBEM) to reconstruct the CO<sub>2</sub>-sensing cpA neuron and its odor-sensitive neighbors, cpB and cpC, within a single capitulum sensillum from a 3-5 day-old adult female *Aedes aegypti*. Morphometric analysis of three reconstructed cpA neurons revealed that cpA possesses an outer dendritic surface area 8-12 times greater than that of cpB and cpC, achieved through the formation of numerous flattened dendritic sheets folded into intricate lamellae. In contrast, cpB and cpC neurons exhibit sparse, narrow cylindrical dendritic branches. Moreover, the cpA axon displays a prominent pearls-on-a-string morphology, with numerous mitochondria-rich, non-synaptic varicosities interspersed with thin cables. Remarkably, a dedicated glial cell and an auxiliary cell together—and exclusively ensheath the cpA soma, suggesting a specialized role in supporting its function. Compared to *Drosophila* CO<sub>2</sub>-sensing ORNs, a larger proportion of the mosquito cpA outer dendrite is embedded within the sensillum cuticle, potentially enhancing access to environmental CO<sub>2</sub>. All tissues were prepared using the CryoChem method to ensure optimal ultrastructural preservation, and the complete SBEM dataset is publicly available (Cell Image Library, CIL:57520) to promote reproducibility. This exploratory study provides the first detailed 3D anatomical characterization of mosquito CO<sub>2</sub>-sensing neurons, revealing morphological specializations that likely contribute to the heightened host-seeking capability of female mosquitoes. Our findings offer new insight into the structural basis of sensory biology and lay the groundwork for future investigations into the mechanisms underlying mosquito olfactory acuity.

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## **Poster**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.06/M6

**Topic:** E.03. The Chemical Senses

**Support:** NIDCD R00 DC017754

**Title:** Plasticity in the olfactory bulb caused by the loss of the calcium activated chloride channel TMEM16B

**Authors:** \*Z. A. FYKE<sup>1</sup>, J. D. ZAK<sup>2</sup>;

<sup>1</sup>Biol. Sci., Univ. of Illinois at Chicago, Chicago, IL; <sup>2</sup>Biol. Sci., Univ. of Illinois Chicago, Chicago, IL

**Abstract:** Sensory circuits rely on faithful encoding of external stimuli by peripheral neurons. In the olfactory system, odorants bind to receptors on olfactory sensory neurons (OSNs), activating a transduction cascade involving cyclic nucleotide-gated (CNG) channels and the calcium-activated chloride channel TMEM16B. TMEM16B amplifies the CNG-mediated depolarization via  $\text{Cl}^-$  efflux, accounting for ~90% of the transduction current (Pietra et al., 2016).

Paradoxically, the loss of TMEM16B results in increased OSN output, as well as changes in odor coding, and impaired olfactory behaviors (Reisert et al., 2024; Belonio et al., 2025). We asked whether the developmental loss of TMEM16B in OSNs induces plasticity at their synaptic targets in the olfactory bulb and downstream cortical structures. To address this question, we performed whole-cell patch-clamp recordings from external tufted cells (eTCs) and mitral/tufted (M/T) cells in WT and *Tmem16b*<sup>-/-</sup> mice. eTCs from *Tmem16b*<sup>-/-</sup> mice showed reduced spontaneous excitatory postsynaptic current (sEPSC) amplitudes (Mean current (pA), WT =  $24.76 \pm 5.11$ , *Tmem16b*<sup>-/-</sup> =  $17.21 \pm 6.03$ ,  $p = 0.0344$ ). M/T cells, however, displayed unchanged excitatory input and increased spontaneous inhibitory postsynaptic current (sIPSC) frequency (Mean event frequency (Hz), WT =  $12.87 \pm 4.26$ , *Tmem16b*<sup>-/-</sup> =  $22.44 \pm 5.34$ ,  $p = 0.0159$ ). Given altered excitatory and inhibitory inputs in the OB of mice lacking TMEM16B, we hypothesized that reduced presynaptic neurotransmitter release could account for the plasticity in eTCs. We used a paired-pulse protocol and found no difference in the paired pulse ratio of eTCs from WT and *Tmem16b*<sup>-/-</sup> mice, suggesting downstream plasticity mechanisms. These findings establish a functional role for TMEM16B in shaping synaptic integration and maintaining excitation-inhibition balance in early olfactory circuits. Ongoing work aims to determine how TMEM16B shapes odorant representations in the OB using 2-photon imaging and may alter downstream input to the piriform cortex.

**Disclosures:** Z.A. Fyke: None. J.D. Zak: None.

**Poster**

**PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.07/M7

**Topic:** E.03. The Chemical Senses

**Support:** R01DC015525  
R01DC022619

**Title:** Functional mapping of olfactory bulb inputs to the anterior olfactory nucleus

**Authors:** \*Q. ZHANG, R. BLAZING, K. M. FRANKS;  
Duke Univ., Durham, NC

**Abstract:** The anterior olfactory nucleus (AON) is the first cortical recipient of olfactory bulb (OB) input and has been implicated in odor processing, localization, memory, and social recognition. Individual AON neurons receive direct excitatory inputs from the ipsilateral OB, as

well as indirect input from the contralateral OB through the contralateral AON and the piriform cortex. However, little is known about the precise structure of connectivity from the OB to the AON. To address this, we optogenetically stimulated the OB of awake, head-fixed mice expressing channelrhodopsin in the olfactory bulb glomeruli (OMP-ChRV<sup>+/+</sup> or Thy1-ChR2<sup>+/+</sup>) with individual glomerulus-sized spots of light while recording extracellularly from populations of AON neurons. Using this approach, we generated a map of stimulation efficacy spanning the dorsal OB for each recorded neuron. We observed that AON neurons could be sorted into three distinct functional connectivity profiles based on the number and spatial distribution of effective stimulation sites: *sparse*, responding to only one or a few sites on the exposed OB surface; *intermediate*, responding to multiple dispersed sites; and *extensive*, responding to broad, contiguous patches on the OB surface. These distinct receptive fields suggest that AON neurons play different roles in processing the spatial structure of OB input. Together, our results reveal how the AON transforms spatially patterned sensory input into diverse response profiles, linking early sensory coding to higher-order olfactory processing.

**Disclosures:** Q. Zhang: None. R. Blazing: None. K.M. Franks: None.

## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.08/M8

**Topic:** E.03. The Chemical Senses

**Support:** DFG CA893/22-1

**Title:** Scent of regeneration: How to train your stem cells

**Authors:** \*V. AVARO<sup>1</sup>, T. HUMMEL<sup>2</sup>, F. CALEGARI<sup>1</sup>;

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**Abstract:** Olfaction is essential for detecting chemical cues, and its partial or complete loss substantially affects our quality of life. Olfactory Training (OT), consisting of repeated short-term exposures to selected odorants, is one of the most effective interventions to treat olfactory dysfunctions, regardless of their etiology. Despite its widespread use, the biological mechanisms underlying OT efficiency remain poorly understood. To address this, we established an OT paradigm in adult wild-type mice that closely models the human treatment. Using EdU labeling, we first characterized proliferation in the peripheral olfactory epithelium and found that OT enhances its proliferative activity, specifically by inducing quiescent horizontal basal cells to enter the cell cycle. Second, by chasing labeled cells, we observed that this proliferative boost ultimately leads to increased neurogenesis. Lastly, in addition to its neurogenic effect, OT also promoted the survival of the pre-existing neuronal population. To further investigate the cellular mechanisms underlying stem cell activation, we generated a transgenic mouse line expressing a

DREADD activator receptor selectively in olfactory sensory neurons. Upon administration of CNO, both the proliferative and neurogenic effects observed with OT were recapitulated, suggesting electrical activity as a key driver of these processes. Collectively, our findings support a model in which OT-induced neuronal activation stimulates stem cell proliferation and neurogenesis, linking peripheral regeneration to the clinical efficacy of OT in restoring olfactory function. Future studies will be needed to determine how this peripheral regeneration influences central olfactory circuits and contributes to the functional recovery observed in patients.

**Disclosures:** V. Avaro: None. T. Hummel: None. F. Calegari: None.

## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.09/M9

**Topic:** E.03. The Chemical Senses

**Support:** R01DC018516

**Title:** Odor exposure enhances the survival and maturation of newborn olfactory sensory neurons

**Authors:** \*S. P. R. BERG, K. CURTIS, C. E. CHEETHAM;  
Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** While neuron loss in mammals is usually irreversible, in the olfactory epithelium, basal stem cells generate olfactory sensory neurons (OSNs) throughout life. Understanding such natural systems of postnatal neurogenesis is crucial in order to effectively develop stem cell-based treatments for both anosmia and neurodegenerative disease. OSNs are responsible for detecting odors and passing that information to neurons in the olfactory bulb (OB) for processing. However, the survival of newborn OSNs is poor and depends on synapse formation with OB neurons. Given that synapse formation is promoted by OSN activity, we investigated the impact of evoked activity in OSNs on their survival and integration into OB circuits. To address survival, we birth-dated newborn OSNs in adult male and female mice using the thymidine analog EdU. We manipulated odor experience for seven or fourteen days by either exposure to an odorant mixture or naris occlusion using a nose plug. We then assessed OSN density in the olfactory epithelium as well as their expression of immature and mature OSN markers. We found that odor exposure increased the survival of newborn OSNs, with more cells reaching both seven and fourteen days of age. It also increased the number of newborn OSNs that reached maturity (expressed OMP) by fourteen days. This suggests that evoked activity may be sufficient to enhance the survival of these stem cell-derived neurons. In contrast, naris occlusion did not affect newborn OSN survival or maturation, suggesting that evoked activity is not necessary for these processes. To address integration into OB circuits, we are using transgenic models that enable selective optogenetic stimulation of either immature or mature

OSNs in adult male and female mice. We are chronically imaging optogenetically-evoked GCaMP6s responses in OB neurons across weeks, to determine whether OSN integration is affected by odor exposure or naris occlusion. This study will reveal the role of evoked activity in the survival and integration of an endogenously generated population of adult-born neurons, which may be useful in designing therapeutic strategies based on stem cell-derived neurons.

**Disclosures:** S.P.R. Berg: None. K. Curtis: None. C.E. Cheetham: None.

## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.10/M10

**Topic:** E.03. The Chemical Senses

**Support:** NIH/NIGMS R01GM148960  
NIH/NIGMS P20GM125508

**Title:** Compensating for vision loss, hyper-olfactory sensing evolved through fluid-flow dynamics at the olfactory pit without increasing the olfactory sensors.

**Authors:** \*N. CHOI<sup>1</sup>, E. RICEMEYER<sup>2</sup>, M. X<sup>2</sup>, Z. ZHANG<sup>3</sup>, M. NIKAIDO<sup>3</sup>, W. WARREN<sup>2</sup>, M. YOSHIZAWA<sup>1</sup>;

<sup>1</sup>Sch. of Life Sci., Univ. of Hawaii at Manoa, Honolulu, HI; <sup>2</sup>Dept. of Animal Sci., Univ. of Missouri, Columbia, MO; <sup>3</sup>Sch. of Life Sci. and Technol., Tokyo Inst. of Technol., Tokyo, Japan

**Abstract:** The evolutionary tradeoff between olfactory receptor (OR) diversification and visual opsin loss (e.g., trichromatic vision gain in primates) has attracted intense interest in sensory evolution and integration research. However, whether this tradeoff is ubiquitous across rapidly evolving vertebrates remains unclear. The presented study tests this hypothesis within a single species, *Astyanax mexicanus* (Mexican tetra), which comprises both sighted surface-dwelling (surface fish) and blind cave-dwelling (cavefish) populations. Previous reports indicated that juvenile cavefish exhibit significantly heightened olfactory sensitivity to amino acids ( $10^2$ - $10^5$ -fold greater than surface fish) while evolutionarily losing opsin genes. Our comparative genomic analysis of one surface and three independent cave populations revealed no increase, but rather a slight reduction, in OR gene numbers in cavefish (142-148 vs. 159 in surface fish), failing to support the vision-olfaction tradeoff in *A. mexicanus*. This raised the question: what drives enhanced olfaction in cavefish? To address this, we employed a multifaceted approach including electron microscopy, micro-CT, snRNA-seq, HCR-FISH, and fluid particle tracking to investigate the hyper-olfactory response to alanine. From these studies, cavefish exhibited: (1) fewer but larger olfactory lamellae; (2) indistinguishable densities in four major classes of olfactory sensory neurons from surface fish; (3) increased motile cilia coverage on olfactory lamellae, consistent with snRNA-seq results indicating higher proportions of ciliated cells in cavefish; (4) slower fluid flow and longer odorant retention times within olfactory pits compared

to surface fish; and (5) the ability to localize alanine sources at low concentrations ( $10^{-10}$  M) as adults, while surface fish could not. In conclusion, our research unveils a novel mechanism for olfactory hypersensitivity evolution in cavefish. Rather than increases in olfactory sensory neurons or OR gene expansion, altered fluid dynamics in the olfactory pits—such as slower and more complex flow patterns that facilitate prolonged interaction with sensory surfaces—enhance sensitivity without compromising time resolution.

**Disclosures:** N. Choi: None. E. Ricemeyer: None. M. X: None. Z. Zhang: None. M. Nikaido: None. W. Warren: None. M. Yoshizawa: None.

## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.11/M11

**Topic:** E.03. The Chemical Senses

**Support:** T32AG000279  
R01AG079193

**Title:** Distinguishing the Olfactory Epithelium using FDA-Approved Dyes & Computational Methods

**Authors:** \*S. A. SUAREZ<sup>1</sup>, E. A. GIBSON<sup>2</sup>, D. RESTREPO<sup>3</sup>;

<sup>1</sup>Univ. of Colorado Anschutz Med. Campus, Denver, CO, CO; <sup>2</sup>Bioengineering, Univ. of Colorado Denver Anschutz Med. Campus, Aurora, CO; <sup>3</sup>Cell and Developmental Biol., Univ. of Colorado, Aurora, CO

**Abstract:** The olfactory epithelium (OE) is a specialized tissue located deep within the nasal cavity that contains stem cells (globose basal cells and horizontal basal cells), supporting cells and olfactory sensory neurons (OSNs) that are responsible for detecting odorants and transmitting olfactory information to the brain. Anosmia is common in aging and can be a symptom of respiratory infections, medication side effects, and some neurological disorders. As humans age, some OE areas undergo neurogenic exhaustion as their OSNs stop being replaced by globose basal cells, leading to patchiness. In other conditions, the OE may be damaged. As a result, the OE exists in patches surrounded by exhausted OE and respiratory epithelia (RE) within the nasal cavity. These patches vary in size and the OSNs are not uniformly distributed throughout, especially in aging and conditions related to olfactory dysfunction. Therefore, the ability to visualize the OE in vivo can assist with assessment of the cause of aging-related anosmia and olfactory dysfunction. It can also assist in observing and quantifying any changes in OE associated with progression or treatments. This project explores the use of FDA-approved dyes to identify the OE and distinguish it from its surrounding exhausted and respiratory epithelia in combination with image processing methods that include texture analysis and machine learning.

**Disclosures:** S.A. Suarez: None. E.A. Gibson: None. D. Restrepo: None.

**Poster**

**PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.12/M12

**Topic:** E.03. The Chemical Senses

**Support:** NIH/NIDCD R01 DC014701

**Title:** Cholinergic modulation of unit phase-locking to gamma oscillations in olfactory bulb slices

**Authors:** \*J. R. CUNNINGHAM, T. A. CLELAND;  
Psychology, Cornell Univ., Ithaca, NY

**Abstract:** The circuitry of the mammalian olfactory bulb transforms broad patterns of chemosensory input, modulated on a behavioral timescale, into a new metric based on the regulation of principal neuron (MTC) spike timing on a gamma-band timescale. We use multielectrode recordings from olfactory bulb slice explants, together with optical stimulation patterns designed to mimic the spatiotemporal properties of odors, to study this transformation in detail and with greater control over input properties than is possible in vivo. Here, we measure the effects of cholinergic neuromodulation on the construction of fine-timescale odor representations based on fictive odor inputs. Horizontal olfactory bulb slices from OMP-ChR2-EYFP (ORC-M) transgenic mice were presented with spatiotemporal patterns of light stimulation designed to implement a homologous series of sequentially similar odorant stimuli. Specifically, each fictive odorant comprised three spots of light, with increasing dissimilarity mapped as progressively increasing changes in these spots' amplitudes and locations. During fictive odor presentations, gamma (30-80 Hz) oscillations were evoked in both control (CTRL) and acetylcholine (ACH) trials. As previously established, fictive odor stimulation induced a significant minority of MTCs, the identities of which correspond to odor quality, to evoke spikes that are phase locked to gamma, whereas activity in other MTCs remained temporally disorganized. We found that a greater proportion of MTCs were significantly phase-locked to gamma under ACH when compared to CTRL trials (i.e., exhibited significant Rayleigh PLV Z scores,  $p < 0.05$ ). Additionally, among significantly phase-locked units, MTCs individually were more sharply phase-constrained under ACH than under CTRL conditions, based on a phase-locking metric correcting for spike count biases ( $Z_{PLV} = 4.06$  for CTRL, 5.41 for ACH). Cholinergic modulation also increased the basal and stimulus-evoked mean firing rates of MTCs, on average, with similar increases observed among phase-locked and non-phase-locked neurons. These findings demonstrate that cholinergic neuromodulation in the olfactory system, often framed as the enhancement and sharpening of afferent odor representations, has a consistent and corresponding effect on odor representations predicated on spike timing regulation and synchronization on the gamma timescale.



**Disclosures:** J.R. Cunningham: None. T.A. Cleland: None.

**Poster**

**PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR221.13/M13

**Topic:** E.03. The Chemical Senses

**Support:** NSF 201427  
NIH GRANT R01DC010915  
NIH GRANT NS109979

**Title:** Utilizing receptor-defined glomeruli to investigate the organization of inhibition in the mammalian olfactory bulb.

**Authors:** \*M. A. HERRBOLDT, M. WACHOWIAK;  
Neurobio., Univ. of Utah Sch. of Med., Salt Lake City, UT

**Abstract:** In sensory systems, inhibition plays a critical role in shaping response features to stimuli, therefore transforming information that is relayed to cortical processing areas. In the early olfactory system, a diversity of inhibitory circuits shape odorant responses, but the functional organization of these circuits remains unclear. Previous work has uncovered that inhibition is odorant-specific and selective, but how is this selectivity organized in relation to receptor and chemical space? Addressing these questions has been challenging due to difficulty in mapping receptor-level responses to principal output neurons and characterizing responses of the same glomeruli across individuals. To address this challenge, we generated three odorant receptor (OR)-tagged mouse lines in which olfactory sensory neurons (OSNs) expressing a given OR also express mKate2. The lines targeted one class I (Or52h2) and two class II ORs (Or10g9b and Or1ad1), and each was crossed with mice expressing genetically encoded calcium reporters in mitral/tufted (MT) cells or OSNs. We probed OR-tagged glomeruli with large odorant panels (40-50) in awake mice to characterize pre- and post-synaptic excitatory and suppressive tuning. The suppressive response spectrum of Or52h2 MT cells showed evidence of both feed-forward inhibition (associated with weak OSN excitation) and lateral inhibition (suppressive responses in the absence of OSN excitation). We tested two alternative models of the organization of lateral inhibition between glomeruli: a nonuniform/random model, predicting variability in the odorants suppressing a given glomerulus across individuals, and a receptor-defined model, predicting stereotypy of suppressive responses relative to odorant and receptor identity. Notably, odorant-driven suppressive responses were stereotyped within and across individuals, supporting the receptor-defined model of lateral inhibition. However, odorant-evoked suppression was less prevalent in the MT cells of the class II (Or1ad1 and Or10g9b) glomeruli. We next asked how inhibition is organized relative to odorant identity and whether lateral inhibitory connections span receptor domains in the olfactory bulb. Class II OSN-activating odorants did not suppress class I Or52h2 MT cells, and we observed domain-specific spatial segregation of MT cell

excitatory and suppressive responses driven by odorant identity. These results suggest that lateral inhibition in the olfactory bulb is not only selective but also targeted to specific receptor-defined glomeruli, heterogeneous across different OR classes, and domain-specific.

**Disclosures:** M.A. Herrboldt: None. M. Wachowiak: None.

## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.14/M14

**Topic:** E.03. The Chemical Senses

**Support:** NIH BRAIN 1R01NS111673  
NIH TR01 5R01DC017876

**Title:** Decoding the olfactory bulb glomerular map by integrating in vivo responses with receptor identity and odorant binding

**Authors:** \*K. SCHOENBERG<sup>1</sup>, Z. DAWOOD<sup>1</sup>, C. SOITU<sup>2</sup>, A. BECALICK<sup>6</sup>, W. G. BAST<sup>3</sup>, D. E. HERNANDEZ TREJO<sup>3</sup>, P. ZNAMENSKIY<sup>6</sup>, A. M. ZADOR<sup>4</sup>, A. KOULAKOV<sup>5</sup>, D. ALBEANU<sup>1</sup>;

<sup>1</sup>Cold Spring Harbor Lab., Cold Spring Harbor, NY; <sup>2</sup>Cold Spring Harbor Lab., Brooklyn, NY; <sup>3</sup>Neurosci., <sup>4</sup>Zador Lab., Cold Spring Harbor Lab., Cold Spring Harbor, NY; <sup>5</sup>Cold Spring Harbor Lab., Cold Spg Hbr, NY; <sup>6</sup>The Francis Crick Inst., London, United Kingdom

**Abstract:** Olfaction remains one of the least understood senses. In vision and audition, key breakthroughs arose from identifying the stimulus dimensions encoded by sensory receptors. For example, color vision relies on three cone photoreceptor types, enabling natural stimuli to be represented as combinations of three primary colors. In contrast, mice express ~1,100 odorant receptors (ORs), and we lack a comprehensive map connecting OR identities to the odorants that activate them. Available OR-odorant affinities are largely derived from in vitro assays and often fail to reflect in vivo sensitivities. Therefore, a critical missing component is an in vivo OR-odorant activation matrix that defines the tuning profiles of each OR/glomerulus.

To this end, we are developing an integrated strategy to map the molecular identity of most ORs to their corresponding glomeruli and to measure responses of dorsal OR/glomeruli to large odorant panels. Using widefield GCaMP6s imaging, we recorded dorsal OB glomerular responses to 62 odorants (1:1000 dilution) in vivo. We then performed BARseq2.0 on the same tissue to detect OR transcripts in 20 µm OB slices. In the same animal, out of ~250 glomeruli on the dorsal aspect of the olfactory bulb, we mapped ~40 unique ORs to their corresponding glomerulus and ~16 ORs to 2-3 glomeruli, potentially reflecting glomerular duplication or padlock cross-reactivity. These 56 OR-glomeruli assignments were consistent with recent OR-to-glomerular mapping efforts, while providing >5 µm spatial resolution (Bintu et al., 2025; Klimpert et al., 2025; Wang et al., 2022; Zhu et al., 2022). Our combined approach enables high-

throughput empirical determination of OR identity and odor tuning. In ongoing experiments, we are expanding our panel of odorants to ~300 per mouse and further mapping OR-ligand affinities by sampling responses across multiple concentrations for each molecule.

In parallel, we are building machine learning models to predict OR-odorant binding. Using AlphaFold3, we predicted 3D structures for 1,109 intact mouse ORs. For the initial training, we used bioassay data from the M2OR dataset, utilizing 315 OR-ligand pairs out of the total 75K available (0.4%) (Lalis et al., 2024). We trained a support vector machine (SVM) using ligand docking-derived features. The model achieved a Matthews correlation coefficient of 0.31 on test data with 10-fold cross-validation ( $p < 0.001$ , bootstrap), demonstrating our model's predictive utility when applied to the entire M2OR dataset.

Together, our efforts aim to enable predictive models of receptor tuning across the OR repertoire and uncover principles linking the odor space to olfactory perception.

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## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.15/M15

**Topic:** E.03. The Chemical Senses

**Support:** DAE, Government of India (Project No. RTI 4007)

**Title:** A novel endoplasmic reticulum chaperone plays an essential functional role in vomeronasal neurons

**Authors:** \*G. DEVAKINANDAN, A. DANI;  
Tata Inst. of Fundamental Res., Hyderabad, India

**Abstract:** Mouse vomeronasal sensory neurons detect chemo-signals important for initiating innate social and reproductive behaviors. Developing from a stem cell population, these sensory neurons differentiate into two subtypes, characterized by the expression of distinct G-protein subunits, (Gai2 or Gao) and G-protein coupled receptor families, (V1R or V2R GPCRs). In our recent study (Devakinandan et al., 2024), we found that Gao neurons exhibit elevated expression of genes encoding endoplasmic reticulum (ER)-associated proteins. Here, we identify Cnpy1 as a novel ER chaperone with restricted expression in Gao neurons. Absence of Cnpy1 leads to a substantial loss of neurons by apoptosis during postnatal development, eliminating more than 50% of V2R expressing neurons and leading to reduced neuronal activation to pheromonal cues, as measured by pS6 labeling. Co-immunoprecipitation followed by mass spectrometry, identified specific interactions of Cnpy1 with V2Rs along with other ER chaperones. Together with our earlier findings of hypertrophic and gyroid ER in Gao neurons, these results highlight a critical

role for both ER-specific genes and ER architecture, necessary for the proper function of vomeronasal sensory neurons.

**Disclosures:** G. Devakinandan: None. A. Dani: None.

## Poster

### PSTR221: Olfaction: Peripheral Mechanisms

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.16/M16

**Topic:** E.03. The Chemical Senses

**Support:** Simons Foundation  
NSF EFRI BRAID: Scalable-Learning Neuromorphics #2318152

**Title:** Sensory Encoding as Coherent-Set Clustering of Dynamic Stimuli

**Authors:** \*D. B. CHKLOVSKII<sup>1</sup>, X. DING<sup>1</sup>, C. EPSTEIN<sup>2</sup>, J. J. MOORE<sup>3</sup>, J. PUGHE-SANFORD<sup>1</sup>, A. SENGUPTA<sup>2,4</sup>;

<sup>1</sup>Ctr. for Computat. Neurosci., <sup>2</sup>Flatiron Institute, Simons Fndn., New York, NY; <sup>3</sup>Neurosci. Inst., NYU Sch. of Med., New York, NY; <sup>4</sup>Rutgers Univ., New Brunswick, NJ

**Abstract:** Natural stimuli unfold along rich temporal trajectories, yet many theories treat sensory neurons as static feature detectors. We propose that neurons instead perform *coherent-set clustering*: partitioning stimulus trajectories in a high-dimensional dynamical state space into sets (or groups) that evolve cohesively over finite intervals and assigning each new input a set *membership index*.

Persistent coherent sets emerge from spectral clustering of the state-evolution (Koopman) operator. In the locally linear regime, computing membership indices for a pair of coherent sets reduces to projecting whitened inputs onto the dominant singular vector of the state-evolution matrix and rectifying the result - leading to a simple, biologically plausible filter-and-rectify implementation. Contracting sets support near-future input prediction, whereas expanding sets support retrospection, implying a functional dichotomy between *predictive* and *retrospective* cell types. The requisite singular vectors can be learned directly from the inputs via past-future canonical correlation analysis, yielding a data-driven and biologically plausible method to learn coherent sets, which generalizes to nonlinear dynamics by embedding stimuli in a suitable feature space.

Our framework explains the scale and shape of temporal receptive fields, the filter-and-rectify neuronal operation exemplified by ON and OFF cells in the visual system, and suggests a predictive-versus-retrospective interpretation for the known segregation of the projection neurons into tufted versus mitral cells of the olfactory bulb and into non-lagged versus lagged cells of the lateral geniculate nucleus. Coherent-set clustering thus emerges as a fundamental computation underlying dynamic sensory processing.

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**Poster**

**PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.17/N1

**Topic:** E.03. The Chemical Senses

**Title:** From Receptor Activation to Percept: A Probabilistic Model of Olfactory Encoding

**Authors:** \*D. A. RAPS<sup>1</sup>, G. M. PIERCE<sup>2</sup>, G. PAPIANI<sup>1</sup>, L. WU<sup>1</sup>, R. ARROYAVE<sup>1</sup>, J. H. BRANN<sup>3</sup>, P. PFISTER<sup>4</sup>;

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**Abstract:** Humans can detect and discriminate many odors, but exactly how this is accomplished is not yet clear. In addition, we still struggle to reliably predict odor quality of odorants and mixtures. The field of olfaction has long attributed the system's perceptual encoding strategy to the combinatorial activation of odorant receptors (ORs) expressed in peripheral olfactory sensory neurons. Here, we sought to better understand how percepts arise as a function of odorant chemistry and receptor activation patterns. We present evidence suggesting an elemental encoding strategy at the olfactory periphery and hypothesize that activation of a single receptor type is sufficient to generate the associated elemental tonality. We examined the relationships between OR activation, measured via dose-dependent responses in a heterologous expression system, and the perceptual descriptors of their ligands by screening a large, diverse chemical library against selected ORs and matching molecular structures to known descriptors from The GoodScents Company. Those dose response curves provide both potency and an efficacy value, which we combined into a single metric of activity per molecule-OR pair. We set a series of activity thresholds to classify each interaction, and then used a Bayesian approach to calculate the probability of a descriptor being associated with an ingredient that activates a receptor above a given threshold. As our classification of activation became more stringent, the probability of a single tonality for each receptor began to dominate the density functions. We examined how the source of the descriptors might influence the result by running the same analysis with a distinct descriptor set of our ingredient catalog and found similar results. This alternate data source aligned OR7A17 to the more specific CEDARWOOD, instead of the broader WOODY, however also brought ambiguity to other terms. This may highlight a fundamental difficulty for olfactory studies, where semantics can have either a clarifying or obfuscating effect. Importantly, we observed how molecules that activate two of the examined ORs are described with the tonalities associated with each individual OR, suggesting an additive model. We posit that each of these receptors' receptive fields are aligned with an elemental encoding strategy whereby each is associated with a singular percept and therefore propose a receptor-centric representation of perceptual space. This work further suggests the goal to predict how new molecules or mixtures

may smell is feasible by utilizing receptor activity. These results also shed new light on how multidimensional olfactory perceptual space may be encoded.

**Disclosures:** **D.A. Raps:** A. Employment/Salary (full or part-time): dsm-firmenich. **G.M. Pierce:** A. Employment/Salary (full or part-time): dsm-firmenich. **G. Papiani:** A. Employment/Salary (full or part-time): dsm-firmenich. **L. Wu:** A. Employment/Salary (full or part-time): dsm-firmenich. **R. Arroyave:** A. Employment/Salary (full or part-time): dsm-firmenich. **J.H. Brann:** A. Employment/Salary (full or part-time): dsm-firmenich. **P. Pfister:** A. Employment/Salary (full or part-time): dsm-firmenich.

## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.18/N2

**Topic:** E.03. The Chemical Senses

**Support:** NET-CSIR Grant 09/0936(13926)/2022-EMR-I

**Title:** Uncovering the peripheral olfactory code using a simple ORN model

**Authors:** \***J. K. GOCHHAYAT**<sup>1</sup>, C. G. ASSISI<sup>2</sup>;

<sup>1</sup>Dept. of Biol., <sup>2</sup>Biol., IISER Pune, Pune, India

**Abstract:** Natural odors are made up of complex mixtures containing many different components. Odor plumes that animals encounter fluctuate rapidly, with concentrations varying across several orders of magnitude. To investigate how olfactory receptor neurons (ORNs) identify odor components in dynamic, temporally varying plumes, we developed a two-step kinetic model of odor transduction integrated with an adaptive integrate-and-fire (adLIF) neuron model.

Odor induced activity in locust ORNs is known to elicit four stereotypical response motifs, termed excitatory, inhibitory, delayed and offset motifs, each exhibiting its unique temporal profile (Kim et al., 2024). Our model could reproduce these characteristic responses. We investigated the role of these motifs in encoding mixture responses both at the level of single ORN and population of ORNs. We show that some aspects of temporal structure of odor mixtures, such as temporal shift between the odor components can be resolved even by a single ORN provided the response of the ORN to each component of the mixture belongs to specific motif pairs. Moreover, our results suggest that single ORNs resolve these differences by not only changing their response strength but also through their response dynamics. Next, we simulated the population response to odor mixtures. We found that the odor evoked response trajectories for a complex plume are markedly different during the early transient phase compared to the late, near-equilibrium phase. Notably, during the transient phase, trajectories are well-separated for different temporal shifts whereas they overlap during the late phase of the odor response. This suggests different kinds of computation during each phase.

Overall, our simulations suggest that the processing of complex olfactory inputs starts at the peripheral layer. ORNs likely play a role in computations like segmentation, odor-categorization and gradient detection in a dynamic odorscape. Which in turn, may offer insights into olfactory navigation and stereo-olfaction.

**Disclosures:** J.K. Gochhayat: None. C.G. Assisi: None.

## **Poster**

### **PSTR221: Olfaction: Peripheral Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR221.19/N3

**Topic:** E.03. The Chemical Senses

**Title:** From Receptor Activation to Percept: Explainable ML for Decoding Olfactory Information

**Authors:** \*G. M. PIERCE<sup>1</sup>, D. A. RAPS<sup>1</sup>, G. PAPIANI<sup>1</sup>, L. WU<sup>1</sup>, R. ARROYAVE<sup>1</sup>, B. LE CALVE<sup>2</sup>, K. OHLA<sup>2</sup>, C. DELAURA<sup>3</sup>, A. DUMER<sup>3</sup>, J. H. BRANN<sup>1</sup>, P. PFISTER<sup>1</sup>;

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**Abstract:** Understanding odor perception remains complex and unsolved due to the intricate encoding of even monomolecular volatiles by the activation of multiple receptors. We hypothesize that each odorant receptor (OR) encodes one facet of olfactory perception and thus molecules that activate multiple receptors also convey multiple olfactory percepts. Using functional characterization of human odorant receptor activity in a heterologous expression system with an array of volatile chemicals, we explored the molecular logic of odor encoding at the periphery. We measured receptor activation via cAMP generated in response to these compounds. We observed that compounds activating a specific receptor also have a key perceptual quality in common. For example, compounds strongly activating OR11A1, include “earthy” as a description in perceptual descriptor datasets irrespective of chemical structure diversity. We trained a random forest model for each receptor on compounds’ perceptual descriptors and asked the model to classify compounds into activators and non-activators. To examine how the model made decisions about receptor activation, we calculated the SHAP (SHapley Additive exPlanations) values for each feature. Our analysis revealed that each OR encodes a distinct aspect of olfactory tonality. For example, the average SHAP values are larger for the descriptor “earthy” in the model that predicts OR11A1 activation. Our analysis also reveals perceptual qualities that are anticorrelated with receptor activation. Comparing compounds described as “woody” with those that are not, we observe that the average SHAP value for “woody” compounds is negative in the OR11A1 model. This indicates a lower predicted likelihood of activation, suggesting that the model classifies “woody” compounds as non-activators. Given these results, we expect that activating a receptor is sufficient to evoke its perceptual quality. Human sensory testing supports this hypothesis, since we found that

increasing concentrations of an OR's activator elicit a stronger perception of the quality. In light of our results, we conclude that each olfactory receptor encodes a facet of olfactory perceptual descriptor space, akin to a labeled encoding line. This finding supports the view that together the olfactory system is capable of combining elemental units of smell to create a perceptual whole. By utilizing this information, the field could make advances in predictions of the olfactive quality of mixtures or previously unseen compounds.

**Disclosures:** **G.M. Pierce:** A. Employment/Salary (full or part-time): dsm-firmenich. **D.A. Raps:** A. Employment/Salary (full or part-time): dsm-firmenich. **G. Papiani:** A. Employment/Salary (full or part-time): dsm-firmenich. **L. Wu:** A. Employment/Salary (full or part-time): dsm-firmenich. **R. Arroyave:** A. Employment/Salary (full or part-time): dsm-firmenich. **B. Le Calve:** A. Employment/Salary (full or part-time): dsm-firmenich. **K. Ohla:** A. Employment/Salary (full or part-time): dsm-firmenich. **C. DeLaura:** A. Employment/Salary (full or part-time): dsm-firmenich. **A. Dumer:** A. Employment/Salary (full or part-time): dsm-firmenich. **J.H. Brann:** A. Employment/Salary (full or part-time): dsm-firmenich. **P. Pfister:** A. Employment/Salary (full or part-time): dsm-firmenich.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.01/N4

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** ANR-23-CE37-0023-01

**Title:** Discrimination between natural vocalizations in noisy conditions: Are they relationships between behavioral performance and the responses of inferior colliculus neurons?

**Authors:** A. MARTIN<sup>1</sup>, C. HUETZ<sup>1</sup>, \***J.-M. EDELINE**<sup>2</sup>;

<sup>1</sup>NeuroPSI, UMR CNRS 9197, Saclay, France; <sup>2</sup>NeuroPSI CNRS UMR 9197, Saclay, France

**Abstract:** Over the last decades, a large number of studies have described the robustness of auditory cortex responses when target stimuli are presented in situations of acoustic degradations such as noise addition, reverberations, vocoding etc... In very few experiments comparisons have been made with the resistance to noise observed from responses of subcortical auditory neurons. In previous experiments performed in anaesthetized guinea pigs (Souffi et al 2020, 2023), we reported that the responses of inferior colliculus neurons were those showing the highest resistance to noise compared to the other auditory structures. To assess whether this resistance to noise is correlated with the animal's behavioral performance, we trained awake, water deprived, CBA/J mice in a discrimination task between two guinea pig vocalizations (two whistles) in a Go/No Go protocol: One vocalization was used as CS+ the other as CS-. The CS+ allowed the mouse to obtain a drop of water if the animal licked a spout during the 5 seconds after the CS+ presentation. Initially, the mice were trained in quiet, and when they reached 80% of correct



performance, they were trained in increasing levels of stationary noise (at SNR of +10dB, 0dB and -10dB), or of cocktail party noise made of the simultaneous vocalizations of a group of guinea pigs. All mice performed above 80% in quiet and in the +10dB SNR, but their performances were decreased at a 0dB SNR and even more at -10dB SNR. Neuronal recordings were collected in these mice, in awake, passively listening conditions. Neuronal recordings were also obtained while the animals were also engaged in the task. As controls, neuronal recordings were obtained from untrained, exposed mice, which were submitted to exactly the same number of vocalizations as the trained mice. These results should allow determining to what extent the activity of inferior colliculus neurons correlates with the behavioral performance in challenging conditions.

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## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.02/N5

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NIH R15DC020847

**Title:** Hdac3 inhibition via rgfp966 enhances auditory discrimination learning of complex vocalizations in a zebra finch model system

**Authors:** A. C. XANDERS<sup>1</sup>, R. ROY<sup>1</sup>, A. PAPAROUSOPOULOS<sup>1</sup>, N. ST JACQUES<sup>2</sup>, S. ELNAWAWI<sup>1</sup>, D. S. VICARIO<sup>3</sup>, M. L. PHAN<sup>3</sup>, \*C. L. PYTTE<sup>1,2</sup>;

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**Abstract:** Speech comprehension requires encoding, storing, and retrieving auditory memories for complex learned vocalizations. Refinement of auditory encoding, shaped by experience, fine-tunes vocal memories used in communication. Epigenetic mechanisms, such as histone acetylation, have emerged as key regulators of such experience-dependent plasticity in sensory systems. In particular, inhibition of histone deacetylase 3 (HDAC3) has been shown to enhance the formation and selectivity of auditory memories. Understanding how HDAC3 inhibition interacts with experience-dependent processing of vocal sounds may guide interventions for language delays and other communication disorders. In prior work, we demonstrated that the HDAC3-specific inhibitor RGFP966 facilitated auditory memory formation and persistence for natural, complex vocalizations in the zebra finch, a model that learns song vocalizations and stores long term memories of vocal signatures. To determine whether RGFP966 improves song discrimination learning we used zebra finches in an operant Go/No-go paradigm. RGFP966 (10 mg/kg in 50 ul vehicle) was injected i.m. daily after each 4-hour operant session until learning criterion was reached. Controls received 50 ul vehicle. Control birds demonstrated increased

correct choices in response to feedback from all trial outcomes: 1) rewarded Go-responses, 2) rewarded No-go responses, 3) punishment after Go errors, 4) punishment after No-go errors. RGFP966-treated birds reached criterion for song discrimination in fewer trials than controls and improved performance only in response to rewarded Go responses and punished Go responses. Thus RGFP966-treated birds selectively learned contingencies of Go songs only, indicating a narrowed stimulus focus, consistent with work demonstrating increased memory specificity in RGFP966-treated rats. RGFP966-treated birds also performed significantly more withholding responses than controls throughout the paradigm. By improving stimulus discrimination and memory specificity, RGFP966 might reduce inappropriate responding. These findings suggest that HDAC3 inhibition via RGFP966 enhanced auditory discrimination learning by accelerating acquisition and also altered feedback-driven learning strategies.

**Disclosures:** A.C. Xanders: None. R. Roy: None. A. Paparousopoulos: None. N. St Jacques: None. S. Elnawawi: None. D.S. Vicario: None. M.L. Phan: None. C.L. Pytte: None.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.03/N6

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** R15DC020847  
Busch Biomedical Grant

**Title:** Assessing age-related decline in auditory memory and behavioral discrimination

**Authors:** B. FUREST CATALDO<sup>1</sup>, A. CHOE<sup>2</sup>, S. RIZAVI<sup>2</sup>, D. S. VICARIO<sup>2</sup>, C. L. PYTTE<sup>3</sup>, \*M. L. PHAN<sup>4</sup>;

<sup>1</sup>Univ. of Massachusetts, Amherst, MA; <sup>2</sup>Rutgers The State Univ. of New Jersey, Piscataway, NJ; <sup>3</sup>Psychology, Queens Col. CUNY, Flushing, NY; <sup>4</sup>Rutgers Univ., New Brunswick, NJ

**Abstract:** Age-related hearing loss significantly impacts speech processing, speaker identification, attention, and overall cognitive abilities. Improved understanding of the neural and behavioral basis of decline in processing complex communication sounds, a defining human characteristic, requires an appropriate animal model. Songbirds provide a fertile model system because they are among the few animals that learn their vocalizations through a process of vocal imitation similar to human speech acquisition, and our laboratory has identified neural substrates in the Zebra finch (ZF) brain that subserve the remembering and discrimination of species specific communication sounds. We now present our approach to the cognitive and neural effects of aging by assessing behavioral discrimination abilities and neuronal memory for salient sounds in aged and young adult ZFs of both sexes. Age-related discrimination abilities are tested in a novel oddball paradigm that quantifies micro-movements that the birds make with their heads in response to a range of both new and familiar sounds. Neuronal memory strength is assessed in

the caudomedial nidopallium (NCM), an auditory cortical analogue, where neurons undergo stimulus-specific adaptation to repeated songs. Responses to familiar stimuli adapt more slowly than to novel stimuli; this adaptation rate, measured as the slope of the decrease in response amplitude as a function of repetition number, provides an index of the familiarity (memory) of the stimuli tested. NCM responses in aged birds showed weaker neuronal memory for sounds heard 20 hours earlier relative to young adults. Behavioral results in the oddball paradigm, where birds make a distinct pattern of head movements when they unexpectedly hear a different song in a sequence of repeating ZF songs, demonstrated the birds' ability to discriminate between sounds that vary in acoustic similarity. This approach, combining an established electrophysiological paradigm with a novel method of behavioral assessment that does not require operant training, offers valuable tools to evaluate the effects of aging on auditory memory and discrimination abilities.

**Disclosures:** B. Furest Cataldo: None. A. Choe: None. S. Rizavi: None. D.S. Vicario: None. C.L. Pytte: None. M.L. Phan: None.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.04/N7

**Topic:** E.05. Auditory and Vestibular Systems

**Title:** Rapid and long-lasting improvements in neural discrimination of acoustic features with passive exposure in a songbird

**Authors:** \*D. S. VICARIO<sup>1</sup>, W. LIU<sup>2</sup>;

<sup>1</sup>Rutgers The State Univ. of New Jersey, Piscataway, NJ; <sup>2</sup>Psychology, Rutgers Univ., Piscataway, NJ

**Abstract:** Our sensory systems must adaptively encode novel and variable information from the external environment in the service of behavior. In auditory encoding, the balance between discriminating auditory objects and generalizing across surface variations must be modulated dynamically to reflect the ongoing acoustic environment. The present study investigates how passive exposure to parametrically varying simple synthetic sounds can lead to enhanced neural discrimination of acoustic features in Zebra finch higher-order auditory cortex (caudomedial nidopallium, NCM), and whether such effects can be long-lasting. We find that multi-unit and single unit responses recorded in awake adult male and female finches with multiple electrodes show dynamic adaptation (sparser responses) that is correlated with increased discrimination between stimuli after passive exposure to these repeated sounds. In addition, these effects generalize to adjacent acoustic features on the stimulus continuum in a way that is proportional to their acoustic distance. Moreover, these exposure effects are partially maintained in testing 4 and 20 hours after exposure. We suggest that response adaptation in a higher-order area of songbirds reflects a process of encoding acoustic features dynamically and efficiently that

improves discriminability in parallel with systematic generalization to similar sounds. These effects can be long-lasting, providing a potential neural mechanism for implicit learning that shows both precision and flexibility that can serve behavior in novel environments.

**Disclosures:** D.S. Vicario: None. W. Liu: None.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.05/N8

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NIH Grant 5R01DC018321-02

**Title:** The neural basis of the transformation from sound to meaning in the songbird auditory system

**Authors:** \*L. THOMAS<sup>1</sup>, F. E. THEUNISSEN<sup>2</sup>;

<sup>2</sup>Psychology, Integrative Biology, Neurosci., <sup>1</sup>UC Berkeley, Berkeley, CA

**Abstract:** Natural auditory processing involves cognitive mechanisms beyond pure acoustic encoding, including attention, prediction, and decision-making. While previous research has characterized neural responses during passive listening, how such cognitive mechanisms transform representations during active behavioral tasks remains poorly understood. The avian auditory system provides an ideal model for investigating this transformation, as zebra finches, a vocal and social species, naturally categorize vocalizations for communication.

We developed novel chronic recording techniques using custom 3D-printed implants housing high density silicon electrode arrays to record from primary auditory area Field L and secondary auditory area NCM in behaving zebra finches. Birds were trained to discriminate between songs from different vocalizers via an operant conditioning task, allowing us to compare task engaged and passive listening states. Neural response properties established during passive listening were preserved during task performance: Field L narrow-spiking neurons maintaining high firing rates and robust envelope tracking, and NCM broad-spiking neurons retained sparse, syllable-specific coding. However, engagement in the operant task produced significant modulations: NCM neurons showed enhanced responses to specific categories during operant conditioning compared to passive playback.

By comparing the accuracy of decoding vocalizer identity from the neural code during trials where the bird makes an error to trials where the bird is correct, we found critical evidence for functional specialization emerging in the auditory system. Decoding accuracy in primary area Field L remained high regardless of behavioral outcome, indicating stable acoustic representations independent of perception. In contrast, decoding accuracy in secondary area NCM degraded significantly on trials in which the bird was incorrect, demonstrating that neural activity reflects the bird's perceptual interpretation rather than physical properties of the

stimuli. These results offer insights into the neural mechanisms underlying the functional transformation from sound to meaning during active perception.

**Disclosures:** L. Thomas: None. F.E. Theunissen: None.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.06/N9

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NIH R01 DC014950  
NIH R21 DC021048

**Title:** Multimodal convolutional neural networks reveal joint encoding of sound and allocentric place in auditory cortex of free-moving ferrets.

**Authors:** \*J. C. WINGERT<sup>1,2</sup>, J. STICKNEY<sup>2</sup>, B. N. BURAN<sup>2</sup>, S. V. DAVID<sup>2</sup>;  
<sup>1</sup>Behavioral and Systems Neurosci., <sup>2</sup>Oregon Hearing Res. Ctr., Oregon Hlth. and Sci. Univ., Portland, OR

**Abstract:** Auditory encoding is almost exclusively studied in head-fixed preparations, out of necessity to control acoustic conditions. In contrast, natural listening is dynamic, as both listener and sound sources can move with respect to one another. A broad range of non-sensory information, including orofacial movements, locomotion, location, and task-related variables, have been shown to be encoded in auditory cortex (AC). Excluding a few studies on simplified cases of refference, the impact of these non-sensory signals during naturalistic listening has not been investigated. To investigate the impact of both explicit acoustic stimuli and non-sensory signals on AC activity during movement, we performed semi-chronic Neuropixel recordings in the AC of four ferrets and used multi-camera tracking while they navigated an arena and performed a sensory detection task. During these tasks, animals had to identify and localize targets in continuous backgrounds of natural sounds presented concurrently from two different locations. Video tracking of head position and angle relative to the sound sources allowed us to virtually head-fix animals and estimate the stimuli reaching the ears via a head-related transfer function. Multimodal convolutional neural network models were fit to predict spiking activity based on aggregate auditory and spatial-motor signals. The multimodal models predicted activity better than models based only on auditory signals. Analysis of residual non-sensory activity showed modulation strongly resembling hippocampal place tuning, with sensitivity to both position and velocity. Place encoding by single units is stable across changing behavioral contexts, as shown by reversing trial initiation and reward locations. Allowing the head-related transfer function to be fit to maximize neural predictions does not remove the presence of positional coding. Also, place coding is still present in animals using headphones for sound presentation and during silent non-auditory periods. Finally, the interaction between sensory and

non-sensory encoding can be described by a simplified model where a gain/offset term is applied to the model's sensory prediction, suggesting a high degree of separability between the signals. How this multimodal code is utilized by downstream perception and behavioral processes remains an open question for future study.

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## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.07/N10

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** Beijing NSF Grant 5232028

**Title:** Auditory Cortical Sensitivity to Infant Vocalizations Underlying Caregiving Behavior in Marmoset Fathers

**Authors:** \*X. ZOU<sup>1,2</sup>, Z. LYU<sup>1</sup>, X. FAN<sup>1</sup>, X. LYU<sup>1</sup>, J. TSUNADA<sup>3,1</sup>;

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**Abstract:** Parental care is essential for the offspring's survival and well-being. A unique feature of human infant care is the involvement of both mothers and fathers, with the latter referred to as paternal care. However, the neural mechanisms underlying paternal care remain poorly understood. This knowledge gap persists because cooperative breeding, where both parents contribute to offspring care, occurs in only ~5% of animal species, limiting the availability of suitable animal models. Marmoset monkeys, a non-human primate species naturally exhibits paternal care in both wild and laboratory settings, provide a rare opportunity to study this behavior. Leveraging this advantage, our study aimed to uncover the neural mechanisms underlying paternal behavior in marmosets. Building on insights from studies of maternal behavior in rodents and infant-retrieving behaviors in marmosets, we hypothesized that sensitivity to infant calls in the auditory cortex of marmoset fathers increases after birth, and this change promotes paternal behavior evoked by these calls. To test this hypothesis, we longitudinally tracked changes in the behavioral and neural sensitivity of marmoset fathers to infant calls. Specifically, we continuously monitored caregiving behaviors within family groups in the housing colony and developed a novel behavioral paradigm to assess responses to infant distress calls in the laboratory. As expected, immediately after birth, marmoset fathers exhibited significantly stronger behavioral responses to infant distress calls compared to other auditory stimuli, such as frequency-matched band-pass noise. Interestingly, these responses gradually attenuated as infants began to spend more time independently in the housing environment, suggesting that paternal behaviors observed in the laboratory reflect naturalistic caregiving dynamics. Consistent with the behavioral findings, auditory cortical responses to infant distress

calls during passive listening increased after birth, particularly in the theta and high-gamma frequency bands of the local field potentials. Importantly, these changes were not observed in neural responses to adult vocalizations or other non-infant-related stimuli, demonstrating a selective enhancement of neural sensitivity to infant-specific stimuli. Together with our preliminary analyses of neural data collected during active engagement in the behavioral paradigm and infant-retrieving tasks, our findings suggest that enhanced neural oscillations in specific frequency bands of the auditory cortex underlie call-induced paternal caregiving behaviors.

**Disclosures:** X. Zou: None. Z. Lyu: None. X. Fan: None. X. Lyu: None. J. Tsunada: None.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.08/N11

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NIH/NIDCD Grant R01-DC018525

**Title:** Sensory Gain Modulation during Vocal Production in Marmoset Auditory Cortex

**Authors:** R. CHOI, \*S. ELIADES;  
Duke Univ. Sch. of Med., Durham, NC

**Abstract:** Vocalization is a sensory-motor process requiring auditory self-monitoring to detect and correct errors in vocal production. During vocal production there is a well-described suppression of neural activity in the auditory cortex. Simultaneously, many neurons exhibit an increase in their sensitivity to experimental perturbations in sensory feedback. The potential neural computations underlying these vocalization-related responses, however, remain unknown. In part, investigation has been limited by the inherent variability in natural vocal production, challenging direct comparison with sensory responses during non-vocal conditions. In this study, we investigated neural activity in the auditory cortex of vocalizing marmoset monkeys, presenting parametrically-varied tone stimuli during vocal production, and comparing responses to similar sounds during passive listening. We found that responses to tone stimuli were reduced during vocalization when compared to tones presented when an animal was not vocalizing, including tones presented with playback of vocal sounds. The effects of vocal production on sensory responses often varied systematically across different tone frequencies, in a fashion suggestive a divisive gain modulation, rather than a subtractive effect of vocal suppression. We did not find any changes in frequency tuning attributable to vocalization. We further evaluated the relationship between responses to individual tone frequencies and the acoustics of the overlapping vocalizations, as well as differences due to neurons' passive receptive fields. These results suggest possible computational mechanisms underlying vocalization-induced suppression, and may suggest possible targets for investigating local cellular and circuit mechanisms, with

implications for our broader understanding of predictive and sensory-motor processes and their effects on sensory coding.

**Disclosures:** R. Choi: None. S. Eliades: None.

**Poster**

**PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR222.09/N12

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** CONACYT CB-256767  
PAPIIT IN229323

**Title:** Neuronal Correlates of Auditory Discrimination in the Frontopolar Cortex of Rhesus Monkeys

**Authors:** \*M. ALVA, T. FIGUEROA, L. LEMUS;  
Inst. de Fisiología Celular, Univ. Nacional Autónoma de México, México City, Mexico

**Abstract:** The frontopolar cortex (FPC), designated as Brodmann area 10, a region unique to primates, is implicated in complex cognitive functions, yet its precise role remains debated. Despite its strong anatomical connections to auditory processing centers in the superior temporal gyrus, studies directly measuring FPC neuronal activity are scarce and have predominantly focused on visual encoding. This gap is particularly notable given the FPC's potential role in auditory processing. To explore its involvement, we trained two rhesus macaques on an auditory discrimination task and recorded FPC neurons extracellularly. We found that the FPC neurons encode distinct learned sounds at single and population level.

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**Poster**

**PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.10/N13

**Topic:** E.05. Auditory and Vestibular Systems

**Title:** Human auditory cortex integrates across similar timescales in music and speech bilaterally



**Authors:** \*Z. LI<sup>1</sup>, T. WYCHOWSKI<sup>3</sup>, W. H. PILCHER<sup>4</sup>, S. V. NORMAN-HAIGNERE<sup>2</sup>;  
<sup>1</sup>Neurosci., <sup>2</sup>Biostatistics & Neurosci., Univ. of Rochester, Rochester, NY; <sup>3</sup>Neurol., Univ. of Rochester, Sch. of Med. and Dent., Rochester, NY; <sup>4</sup>Div. Neuroendocrinol, Univ. Rochester Sch. Med., Rochester, NY

**Abstract:** Human auditory cortex integrates across similar timescales in music and speech bilaterally

Integrating information across the complex temporal structure that defines music and speech is one of the central challenges of human hearing. Many theories propose distinct neural integration timescales for music and speech, reflecting their differing acoustic and temporal properties. However, no studies have directly estimated integration windows for speech and music in the human auditory cortex, in part due to the challenge of measuring integration windows from nonlinear systems like the brain using coarse, non-invasive neuroimaging methods. To overcome this challenge, we measured integration windows from the human auditory cortex using spatiotemporally precise intracranial recordings from neurosurgical patients coupled with a recently developed method for estimating integration windows from nonlinear (and linear) systems (the Temporal Context Invariance (TCI) paradigm). The TCI paradigm identifies the shortest segment duration for which neural responses remain invariant across varying contexts and does not make any assumptions about stimulus features that underlie the response or the stimulus-response mapping (e.g., linear or nonlinear). Consistent with prior findings, we observed that neural integration windows substantially increase as one ascends the cortical hierarchy from primary to non-primary auditory cortex bilaterally. However, we find that integration windows were very similar for speech and music stimuli across both primary and non-primary auditory cortex in both the left and right hemisphere. These findings suggest that neural integration windows do not change substantially with the category of sound, and thus that information in music and speech is integrated using similar temporal windows.

**Disclosures:** Z. Li: None. T. Wychowski: None. W.H. Pilcher: None. S.V. Norman-Haignere: None.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.11/N14

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** This project is funded by a PhD-fellowship of the University of Oslo

**Title:** Social traits influence behavioral and neural responses to emotional AI and human voices

**Authors:** \*C. L. SKJEGSTAD<sup>1</sup>, L. ABRAHAMSSON<sup>1</sup>, S. FRUEHHOLZ<sup>2</sup>;

<sup>1</sup>Univ. of Oslo, Oslo, Norway; <sup>2</sup>Dept. of Psychology, Univ. of Zurich, Zurich, Switzerland

**Abstract:** Individual differences tint our perception of reality. Our previous work showed certain personality traits influence how the brain responds to human voices. Recently, we found the brain responds differently to voices generated by artificial intelligence (AI) compared to human voices, despite challenges in perceptual discrimination. This study investigates whether social traits further influence differential neural processing of AI and human voices. 61 participants (40 females, mean age = 31.93,  $SD = 7.75$ ) listened to vocal emotional pseudo-speech expressions (neutral, angry, fear, happy, pleasure) from both AI-generated and human sources. The protocol included an fMRI study with a classification task, followed by a perceptual task, as well as personality trait assessments. Traits related to social and emotional cognition (Callous-Unemotional [CU], Alexithymia [ALX], Affective Empathy [AE], and Social Information Processing [SIP]) were selected. Correlations between the traits and outcome measures were performed ( $p < 0.05$ , FDR corrected). ALX correlated with a tendency to classify voices as AI ( $r = -0.26$ ) while SIP correlated with a tendency to classify voices as human ( $r = 0.3$ ). AE and SIP were positively correlated with perceived naturalness of human voices ( $r = 0.32$  and  $r = 0.27$ ). Conversely, ALX and CU were negatively associated with perceived naturalness of human voices ( $r = -0.28$  and  $r = -0.28$ ). CU negatively correlated with perceived naturalness of AI voices ( $r = -0.28$ ), whereas AE positively correlated with it ( $r = 0.29$ ). Our fMRI multiple regression analysis included the traits with age, sex, and handedness as covariates of no interest ( $p < 0.005$ ,  $k > 21$ ). Our findings reveal distinct neural patterns: in response to AI voices (versus human), AE was associated with increased activity in the left angular gyrus, left inferior frontal gyrus-triangular part, left hippocampus, right nucleus accumbens and bilateral amygdalae. SIP was associated with increased activity in the right dorsolateral superior frontal gyrus. In response to human voices (versus AI), AE was associated with increased activity in the left precentral gyrus, while CU was associated with increased activity in the bilateral precentral gyri. SIP was associated with increased activity in the right cuneus, right superior temporal gyrus, right fusiform gyrus, left middle cingulate and paracingulate gyri, left insula, and bilateral middle occipital gyri. When processing AI voices, AE may relate to emotional engagement and SIP to more cognitive effort. In the context of human voices, AE and CU may differentially engage the mirror neuron system, while SIP may engage multimodal processing.

**Disclosures:** C.L. Skjogstad: None. L. Abrahamsson: None. S. Fruehholz: None.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.12/N15

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NIH Grant 1R01DC018579

**Title:** Direct Brain Recordings Showing Neural Prioritization of Speech Over Music in Children

**Authors:** \***R. AGRAVAT**<sup>1</sup>, M. DESAI<sup>1</sup>, G. FOOX<sup>2</sup>, A. FIELD<sup>1</sup>, S. GEORGES<sup>2</sup>, J. LEISAWITZ<sup>2</sup>, A. ANDERSON<sup>2</sup>, E. C. TYLER-KABARA<sup>3</sup>, H. L. WEINER<sup>2</sup>, A. WATROUS<sup>4</sup>, L. S. HAMILTON<sup>1</sup>;

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**Abstract:** Our brains are constantly filtering incoming sounds to understand our environment. Are some temporal lobe areas more selective to certain sound streams? While extensively studied in adults, understanding how auditory stream selectivity develops and matures throughout childhood remains a critical gap in our knowledge. Using intracranial stereo-electroencephalography (sEEG), we investigated this question by presenting 51 participants (ages 4-22, 29M/23F, over 8000 electrodes total, with over 1000 temporal lobe electrodes total) with audiovisual movie trailers that contained both speech and music. We extracted and analyzed high gamma band activity (70-150 Hz) to index local neural firing. Data were analyzed using a computational source-separated STRF analysis. We used deep neural networks to decompose the mixed speech-music stimuli into isolated speech and music components, then built separate encoding models for each condition (speech only, music only, and original speech-music mixture). Although the participants heard only the original speech-music mixture and were not directed to attend to any particular stream, STG activity was significantly better modeled by speech only compared to the original mixed and music only models ( $p < 0.0004$  for both comparisons). There was a significant relationship between development stage and brain region ( $p < 0.0001$ ), with STG showing the strongest developmental increase in speech selectivity, indicating that the pediatric brain has an intrinsic neural bias toward socially relevant auditory information that emerges early and strengthens throughout development. We show that different brain regions implicitly attend to specific components of mixed auditory streams, with specialized temporal lobe networks enabling the separation and processing of speech and music simultaneously, even in the absence of explicit attentional directives. This suggests that prioritization of speech may occur through bottom-up, automatic, stimulus-driven processes, rather than a purely conscious, top-down mechanism. These results have significant implications for understanding developmental communication disorders and may inform targeted therapeutic interventions for children with auditory processing deficits.

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## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.13/N16

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NIHR-UCLH Biomedical Research Centre 'Hearing Health' Theme

**Title:** Role of sound offsets and onsets in cortical tracking of transient events during naturalistic speech listening

**Authors:** A. SIMON, M. CHAIT, \*J. F. LINDEN;  
Ear Inst., Univ. Col. London, London, United Kingdom

**Abstract:** The amplitude envelope of speech is crucial for comprehension, and cortical activity in the theta-delta bands has been shown to track this envelope. The hypothesis underlying this tracking is that it reflects the cumulative response to transient events in the speech signal, such as sound onsets (rapid increases in sound amplitude) and offsets (rapid decreases in sound amplitude). While onset tracking has been widely studied, offset tracking remains under-explored.

Here we analyzed the roles of onsets and offsets in cortical speech tracking using two datasets from different laboratories, consisting of continuous EEG recordings from British (n=18) [1] and Danish (n=22) [2] participants listening to audiobooks. We used an onset/offset model based on thalamic responses to sound transients in mice [3] to extract separately the onsets and offsets present in continuous speech. To assess the contributions of these transient sound events to the cortical response, we estimated Temporal Response Functions, which are weights for a linear model that maps continuous stimuli to neural activity. We trained models using the representations of onsets, offsets, or a combination of both, and compared the performance of the models by correlating the measured EEG with the EEG predicted by the linear models.

All models—those trained on onsets, offsets, and the combined onset-offset representation—demonstrated significant performance above chance levels (with  $p < 0.001$ ). This finding indicates that both onsets and offsets contribute to the neural response when listening to speech. Notably, Wilcoxon tests used to compare prediction accuracy between different models across participants showed that models trained on onsets had higher prediction accuracy than those trained solely on offsets ( $p < 0.001$ , Cohen's  $d = 0.69$ ), suggesting that amplitude increases have a more substantial impact than decreases. However, the combined model outperformed both the offset-only ( $p < 0.001$ , Cohen's  $d = 0.85$ ) and onset-only ( $p < 0.001$ , Cohen's  $d = 0.56$ ) models, underscoring the complementary role of sound offsets in cortical speech tracking.

Overall, our results suggest that cortical tracking of speech during continuous listening is driven by the neural responses to transient changes in sound amplitude, with sound onsets playing a dominant role while sound offsets also significantly contribute to the cortical response.

[1] Etard O & Reichenbach T (2022). 10.5281/zenodo.7086208

[2] Simon A, Bech S, Loquet G & Østergaard J (2022). 10.5281/zenodo.7500806

[3] Anderson LA & Linden JF (2016). J Neurosci 36(6), 1977-1995.

**Disclosures:** A. Simon: None. M. Chait: None. J.F. Linden: None.

## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.14/O1

**Topic:** E.05. Auditory and Vestibular Systems

**Title:** Naturalistic speech perception simulators using DNN models

**Authors:** \*P.-T. B. LIU;  
Academia Sinica, Taipei, Taiwan

**Abstract:** Several studies have developed Deep Neural Network (DNN) models to mimic one function of human auditory perception; however, the ultimate goal is a unified model to simulate human auditory perception under various hearing conditions, even simulate high-level functions, e.g. naturalistic speech perception. To this end, I proposed a speech perception simulator, an encoding-decoding framework utilizing auditory modeling and decoding models using DNN. Decoding models should be able to reconstruct perceived sound from the output of simulated auditory nerves' activities. Sound reconstruction from auditory spike trains remains unsolved until my recent decoding work. This research problem can date back to a scientific abstract from the 2012 Bernstein conference. In this sound reconstruction task, the decoding model should use only spiking activities of simulated auditory nerves without additional auxiliary input, such as the signals from the efferent pathways. In 2015 and 2024, the research teams in the U.S. proposed decoding models using algorithms in signal processing, but their results were not realistic enough to proceed with further experiments or simulations, or to draw significant conclusions. My reconstruction models have solved this long-standing unsolved research problem in auditory computational neuroscience. The sound reconstruction models were trained on the dataset with auditory neurograms as input, without any auxiliary input, and sound waveforms as output. Auditory neurograms were computed using Raymond Meddis' Matlab Periphery model on the LJSpeech dataset. My decoding models are neural vocoder-based. To evaluate decoding models, the first 20 sound files were not included in training and were used to compute objective metrics, e.g. PESQ for speech quality. As a result, my models can achieve more than average PESQ score of 4.096, while other baseline models on the same reconstruction task achieved average PESQ scores of around 1.5 or below 3.398. Thus, my decoding models can reconstruct high fidelity sound and make this simulation framework practical to use. This speech perception simulator will enable researchers to answer hypothetical research questions, especially those that are difficult to manipulate in animals or humans. Using this simulation framework, researchers can manipulate auditory nerves' properties or adjust the parameters of auditory models to investigate their effects on auditory processing. For example, my previous study examined the impact of eliminated phase-locking of auditory nerves' on naturalistic speech perception. More experiments using this framework are underway and may be presented at the conference.

**Disclosures:** P.B. Liu: None.

**Poster**

**PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.15/O2

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NIH Grant GR533858

**Title:** Modelling cortical tracking of speech that is robust to variability in speech rate and temporal regularity

**Authors:** \*A. DURAN<sup>1</sup>, A. R. NIDIFFER<sup>1</sup>, W.-C. LIN<sup>1</sup>, Z. LI<sup>1</sup>, S. V. NORMAN-HAIGNERE<sup>2</sup>, E. C. LALOR<sup>1</sup>;

<sup>2</sup>Biostatistics & Neurosci., <sup>1</sup>Univ. of Rochester, Rochester, NY

**Abstract:** Speech is a highly dynamic signal with rich acoustic structure. What operations the brain uses to convert this acoustic structure into robust semantic and syntactic representations remains unclear. The fact that brain activity reflects the acoustic dynamics of speech (speech “tracking”) is something that has been widely used to better understand speech processing, attention, and multisensory integration - including via the use of Temporal Response Function (TRF) encoding models. The transient characteristics of TRFs suggest that speech tracking primarily derives from the summation of transient evoked responses. On the other hand, it has been argued that an optimal way for the brain to parse and track speech into linguistic units is through the entrainment of ongoing intrinsic oscillations. While both frameworks have led to insights into speech neurophysiology, the field lacks clarity on the degree to which each mechanism contributes to speech comprehension. Here, we aim to clarify this by directly testing the ability of both frameworks to account for brain responses to natural speech. In a first set of experiments, EEG was recorded from 18 participants as they listened to audiobooks whose speech rate was manipulated. We then compared the dynamics of TRFs computed from the EEG recorded under different rate conditions. In a second set of experiments, we manipulated the temporal regularity of syllables in the same stimuli, producing speech with the same median speech rate but different overall temporal statistics. One condition had nearly isochronous syllables (regular speech), while the other had more fast and slow syllables (irregular speech). Unaltered speech was used as a control condition (natural speech). Both regular and irregular speech were intelligible and resulted in robust cortical tracking. We examined whether models of oscillatory entrainment - optimized to predict the brain data from each condition - could explain cortical tracking. TRFs estimated from simulated EEG generated by these oscillatory models differed from real EEG, suggesting that the oscillatory entrainment models we tested do not represent real neural activity. To test whether oscillatory entrainment may play a role in more spatially confined regions of auditory cortex less visible to scalp EEG, we repeated this analysis using intracranial EEG from neurosurgical patients. These data show qualitatively similar results. Finally, acknowledging that both mechanisms may play a role in speech processing, we model brain responses using TRFs and entrained oscillators in together to see whether accounting for oscillatory entrainment improves predictive accuracy.

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**Poster**

**PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR222.16/O3

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** IBACS Seed Grant

**Title:** Alpha oscillations differentially reflect attended acoustic and distracting stimuli during naturalistic speech processing

**Authors:** \*T. J. HARLOW<sup>1</sup>, L. ALMOTWALY<sup>2</sup>, H. L. READ<sup>3</sup>;

<sup>1</sup>Univ. of Connecticut, Willimantic, CT; <sup>2</sup>Behavioural Neurosci., <sup>3</sup>Univ. of Connecticut, Storrs, CT

**Abstract:** Alpha-band oscillations (~7-13 Hz) have been implicated in the suppression of irrelevant sensory information, supporting goal-directed behavior in complex auditory scenes. While previous research has associated increased alpha power with anticipatory suppression of distractors (Bonnefond et al., 2017; Foxe et al., 2011), its role in naturalistic, speech-in-noise remains underexplored. In this study, we examined how individualized alpha oscillations are modulated during a digit-in-noise (DIN) task using six naturalistic background sound types with embedded foreground speech at +3db Signal to Noise Ratio (SNR). Thirty-three healthy young adults were tasked with ignoring background sounds while attending to and recalling foreground speech digits. In line with previous research (Dimitrijevic et al., 2017, 2019), we find that alpha activity is differentially modulated by distracting and attended sounds across all background conditions. Specifically, we find alpha power increases with onset of the to-be-ignored background sounds and decreases with onset of to-be-attended foreground speech. Further, we independently estimated distractor and target sound Temporal Response Functions (TRFs), using the optimized attention decoder developed by O'Sullivan and colleagues in 2015 (O'Sullivan et al., 2015). Using the estimated TRFs, we find that N100 amplitudes were selectively attenuated for incorrectly recalled target digits. In future work, we are primarily looking to implement different speech-to-noise ratios to investigate the correspondence of changes in induced alpha power with correct and incorrect recall of target speech segments.

**Disclosures:** T.J. Harlow: None. L. Almotwaly: None. H.L. Read: None.

**Poster**

**PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.17/O4

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NSF Grant 2319491

**Title:** Performance feedback shapes neural encoding during nonnative speech sound learning

**Authors:** \*A. QIN, D. LEE, M. K. LEONARD;  
Univ. of California, San Francisco, San Francisco, CA

**Abstract:** While the brain is highly adept at learning new skills implicitly, challenging tasks like adult language acquisition benefit from feedback that provides explicit guidance on performance. The ways in which feedback from previous trials is related to changes in neural encoding during learning are unclear. Here, we asked how specific trial-by-trial corrective and reinforcing feedback predicts subsequent behavior and neural encoding using high-density direct brain recordings in English-speaking neurosurgical participants while they learned to identify Mandarin Chinese tones. Participants listened to Mandarin syllables that varied in lexical tone (T1: high-flat; T2: high-falling; T3: low-dipping; and T4: low-rising), pressed a button to report which tone they heard, and received visual feedback to indicate accuracy. No additional rewards or penalties were used to signal performance. We found three types of neural populations: (1) exclusively feedback-responsive, (2) exclusively stimulus-responsive, and (3) feedback- and stimulus- responsive. All populations were widely distributed across the cortex, with stimulus-responsive and stimulus-and-feedback-responsive populations located primarily in superior temporal gyrus, and feedback-responsive populations concentrated in orbitofrontal and cingulate cortices. The co-localization of stimulus and feedback encoding suggests an important role for integrated coding of both sensory input and trial-by-trial behavioral performance during learning. To understand how feedback influences encoding in these populations, we compared the effects of receiving corrective versus reinforcing feedback on the previous trial. Preliminary results suggest that corrective feedback changes the encoding of multiple tones, potentially reorganizing the representation of the entire stimulus space, whereas reinforcing feedback primarily affects individual tones, likely strengthening the association between each tone and its correct label. Furthermore, we examined the dynamics of feedback modulation across trials and found that subsequent stimulus encoding was influenced not only by immediate feedback, but also by an extended history of feedback. Specifically, runs of corrective feedback had a distinct effect on the subsequent encoding of the stimulus compared to sequences of trials that alternated between corrective and reinforcing feedback. Together, these results show that by linking past performance to present sensory encoding, feedback-driven modulation offers a possible mechanism through which feedback promotes plasticity in the adult brain during non-native speech sound learning.

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## **Poster**

### **PSTR222: Auditory Processing of Vocalizations and Complex Sounds**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR222.18/O5

**Topic:** E.05. Auditory and Vestibular Systems

**Support:** NIH 1R15DC021563-01



**Title:** Improving sentence and syllable perception using a spatial-segregation algorithm

**Authors:** R. GATEWOOD, A. LE, J. E. ORR, K. PINKHAM, I. GOKCEN, \*Y. GAI;  
St. Louis Univ., Saint Louis, MO

**Abstract:** Hearing-aid users often face significant challenges in locating sound sources and distinguishing individual sounds in noisy environments due to time, level and spectral cues being compromised by current-generation hearing aids. Our project seeks to develop hearing-aid algorithms to improve speech intelligibility by recovering these spatial cues and using them to isolate sound sources. Here we adapted a robotics-based sound localization algorithm for use with multiple simultaneous sound sources. This algorithm can create distinct clusters in a new complex plane that represents the spectrotemporal characteristics of sound mixtures (e.g., speech and noise). Next, binary masks were generated to separate speech from background noise. In Experiment I, the target was 200 intelligible sentences spoken by a female. The noise was time-reversed sentences spoken by the same female speaker. Dragon Automatic Speech Recognition (ASR) software was used to compare speech intelligibility before and after applying our algorithm. The ASR showed highly significantly improved speech-recognition scores for both front and back hemifields, but not for the side (e.g., 90 degrees to the right). In Experiment II, target sounds were syllables containing 8 vowels and 16 consonants spoken by male or female and the background noise was randomly arranged sentences. After applying the algorithm, human subjects' ability to detect the correct vowel/consonant significantly improved. Our findings offer promising insights into the development of more advanced hearing-aid technologies.

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## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.01/O6

**Topic:** E.06. Vision

**Support:** Samsung Science and Technology Foundation (SSTF-BA2302-07)  
National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2024-00358070, RS-2024-00413689, RS-2023-00301976)  
Seoul National University New Faculty Startup Fund

**Title:** Neural variability structure in primary visual cortex is optimized for consistent representation of visual similarity

**Authors:** \*J. KIM<sup>1</sup>, H. SHIN<sup>2</sup>;

<sup>1</sup>Sch. of Biol. Sci., <sup>2</sup>Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

**Abstract:** How different neuronal populations construct a robust representation of the sensory world in the presence of neural variability is a mystery. We found that neural variability in mouse primary visual cortex observe a simple rule: For a given sensory stimulus, the mean and the variance of spike counts follow a linear relationship across neurons. To understand how this neural variability structure affects the sensory representation, we artificially varied the slope of the log-mean and log-variance relationship. We found that the structure of neural variability allows representations of distinct sensory information to be continuous while minimizing overlap, balancing the tradeoff between generalizability and discriminability. Further, representational similarity was most consistent between different sets of neurons, both within and across mice, when the slope was 1. These results suggest that the structure of neural variability may enable different brains to build a common representation of the sensory world.

**Disclosures:** J. Kim: None. H. Shin: None.

## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.02/O7

**Topic:** E.06. Vision

**Support:** NIH Grant RF1MH128672  
Sandler Program for Breakthrough Biomedical Research, which is partially funded by the Sandler Foundation

**Title:** Depth-dependent differences in visual stimulus decoding across layers of mouse primary visual cortex

**Authors:** \*N. DONOVAN<sup>1</sup>, A. SHERAFATI<sup>1</sup>, R. FARHOODI<sup>1</sup>, J. D. LARKIN<sup>2</sup>, K. TAKASAKI<sup>2</sup>, D. WYRICK<sup>2</sup>, J. ZHUANG<sup>2</sup>, D. MILLMAN<sup>2</sup>, D. J. DENMAN<sup>2</sup>, J. LECOQ<sup>2</sup>, A. ARKHIPOV<sup>2</sup>, N. W. GOUWENS<sup>2</sup>, J. WATERS<sup>2</sup>, R. REID<sup>2</sup>, S. E. DEVRIES<sup>2</sup>, M. A. BUICE<sup>2</sup>, R. ABBASI-ASL<sup>1</sup>;

<sup>1</sup>UCSF, San Francisco, CA; <sup>2</sup>Allen Inst., Seattle, WA

**Abstract:** How cortical layers differ or overlap in terms of their neural computations is crucial to understanding cortical function, but remains poorly understood. Here, we used the Allen Brain Observatory V1DD dataset where GCaMP6s transgenic mice were imaged using two-photon and three-photon calcium imaging to record visual responses from excitatory neurons in an ~800 x 800 x 800  $\mu\text{m}^3$  region of mouse primary visual cortex (V1). The data spans all layers from pia to white matter, containing data from 88,351 unique neurons in four mice. Visual stimuli were used to characterize neural responses, including locally sparse noise, full-field and windowed drifting gratings, natural images, and natural movies. Here, we focus on population-level decoding of stimulus identity across cortical depth. A previous study showed that there are broad differences in decoding accuracy between areas and layers in visual cortex (Kong et al., 2023), and we

aimed to look more closely into differences among excitatory neurons at a wider range of depths within V1. We used a k-nearest neighbors classifier to predict features of the visual stimulus identity from a fixed-size bootstrapped sample of the neural population mean responses. We first trained a k-nearest-neighbors classifier to predict the direction of a full-field drifting grating and found that the performance peaked around a depth of  $\sim 258 \mu\text{m}$ , roughly corresponding to the upper part of layer 4. Interestingly, a k-nearest-neighbors classifier trained to predict the image index from a set of natural scenes (set 2; 12 unique images) showed peaks at  $\sim 114 \mu\text{m}$  and  $\sim 450 \mu\text{m}$ , corresponding to about layer 2/3 and layer 5, respectively. Overall, differences in decoding accuracy varied by depth and stimulus identity, with neurons in upper layer 4 best at decoding full-field drifting grating direction while neurons in layer 2/3 and layer 5 best at decoding natural image identity. These findings suggest that different cortical layers may be specialized for distinct representational goals, supporting a departure from a strictly feedforward canonical cortical hierarchy, with mid-depth layers emphasizing bottom-up sensory driven representations and superficial/deep layers contributing to inference or integration across stimulus features and contexts.

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## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.03/O8

**Topic:** E.06. Vision

**Support:** DFG Emmy Noether VE 938/2-1  
DFG CRC-TRR 384/1 39/1422-1

**Title:** Uncovering inter-areal dynamics in mouse visual cortex using deconvolution and non-linear co-activation analysis

**Authors:** \*R. SHANKAR, D. ERIKSSON, C. RAMANATHAN, J. VEIT;  
Inst. of Physiol., Freiburg, Germany

**Abstract:** Fundamental to the precise execution of various brain functions is the selective yet flexible communication of relevant patterns of activity across distributed brain areas. The latero-medial (LM) area in mice is reciprocally connected with the primary visual cortex (V1). However, the nature of the functional relationship between the two areas remains unclear. Here, we introduce a novel analysis method involving a combination of linear deconvolution and nonlinear co-activation analysis (NCA), that is simple, effective and generalizable, and utilize it to dissect the interactions between V1 and LM.

Using a variety of visual stimuli and optogenetic perturbations, we leveraged paired high-density Neuropixels recordings in matched receptive fields in V1 and LM. We first apply linear deconvolution to the population-level spiking activity in V1 and LM, extracting a convolution kernel that provides a direct measure of communication strength, the temporal lag between the regions, and the integration duration of LM for spikes from V1. We combined this with a new technique we term nonlinear co-activation analysis (NCA), wherein, we binned V1 activity into discrete levels, and observed the average LM activity for each V1 activity level, giving us a measure of the nonlinearity in the shared activity of the two regions.

With this approach, we observe clear differences in communication across various stimulus conditions. A similar V1 activity was associated with differentially higher LM activity, as the stimulus contrast increased. Additionally, increasing stimulus size increases feedforward inter-areal gain, despite V1 firing rates reducing with increasing size. We also observe differential nonlinear co-activation effects with varying amounts of multiplicative and additive gain depending on both stimulus size and contrast. High-contrast, spatially extensive stimuli also induce pronounced synchronization in V1 circuits. Taken together, this could point to the potential role of synchrony in facilitating inter-areal communication, with relevant information propagating and driving LM activity despite reduced V1 population activity.

By combining deconvolution and NCA, we provide fresh perspectives on inter-areal communication. Our novel technique is elegant, effective at teasing out both feedforward, and feedback interactions, and generalizable to other multi-areal recordings. We also hope to uncover the role of specific cell types and laminar influences on inter-areal communication, allowing us to refine our understanding of distributed functional connectivity in the mouse visual system and their modulation by sensory and artificial input.

**Disclosures:** R. Shankar: None. D. Eriksson: None. C. Ramanathan: None. J. Veit: None.

## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.04/O9

**Topic:** E.06. Vision

**Support:** NIH Grant EY026286  
NIH Grant EY020950  
NIH Grant EY032360  
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**Title:** Synergistic geniculate and cortical dynamics facilitate a decorrelated spatial frequency code in the early visual system

**Authors:** \*A. ELSAYED<sup>1</sup>, R. J. SKYBERG<sup>2</sup>, J. CANG<sup>3</sup>, C. MELIZA<sup>4</sup>;

<sup>1</sup>Univ. of Virginia, Charlottesville, VA; <sup>2</sup>Biol., Univ. of Oregon, Eugene, OR; <sup>3</sup>Biol.,

<sup>4</sup>Psychology, Univ. of Virginia, Charlottesville, VA

**Abstract:** The primary visual cortex (V1) encodes spatial frequency (SF) information through decorrelated population responses that enhance discrimination between visual features and improve encoding efficiency. Decorrelation is thought to be driven by a SF tuning shift from coarse to fine features emerging in upstream dorsal lateral geniculate nucleus (dLGN). However, whether decorrelation is inherited from dLGN, driven by local activity in V1, or the result of synergy between these areas is unknown. To reveal how and where decorrelation emerges, we took multielectrode recordings from single units in dLGN (n = 237) and V1 (n = 259) of adult mice (10 for dLGN; 15 for V1, aged P40-P90) and used subspace forward correlation to obtain response profiles to a series of sinusoidal gratings of varying SF (0.02-0.32c/d). We computed the correlation between each pair of SF-evoked response vectors across time. The level of correlation in V1 population activity decreased from an early (78 ms) to late (111 ms) time point (GLMM:  $z = 12.3$ ,  $p < 0.001$ ), and such a decorrelation did not occur in dLGN (GLMM:  $z = 1.27$ ,  $p = 0.58$ ). In contrast, most units exhibited a positive shift in SF tuning in both areas (dLGN = 61%,  $X^2 = 11.85$ ,  $p < 0.001$ ; V1 = 84%,  $X^2 = 120.96$ ,  $p < 0.001$ ), confirming that coarse-to-fine processing was insufficient to explain decorrelation and that decorrelation emerges in V1. Furthermore, we observed a coordinated increase in SF selectivity across most units in the V1 population ( $\mu$ -selectivity =  $0.69 \pm 0.01$ ) which appeared to be mediated by broadly tuned nonlinear suppression. However, the peak of SF selectivity in the population average (~143 ms) did not coincide with the valley of SF-response vector correlations (~111 ms). Therefore, nonlinear suppression in V1 was also insufficient to explain decorrelation, suggesting that decorrelation was not an entirely local phenomenon. Finally, we considered whether coarse-to-fine processing shifts SF responses in time while nonlinear suppression shifts responses in amplitude such that high SFs enhancement coincides with low SF suppression across the V1 population, reducing correlations at longer lags. Using an enhancement/suppression index, we found that the balance of enhancement and suppression shifted toward enhancement for high SFs and suppression for low SFs precisely at the time when correlations across the V1 population reached their minimum. We have therefore identified a cortical computation requiring synergy between upstream coarse-to-fine dynamics from dLGN and local nonlinear suppression in V1. This geniculocortical interaction drives the decorrelated population code essential for visual discrimination.

**Disclosures:** A. Elsayed: None. R.J. Skyberg: None. J. Cang: None. C. Meliza: None.

**Poster**

**PSTR223: Visual Cortex: Population Recording and Analysis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.05/O10

**Topic:** E.06. Vision

**Support:** Howard Hughes Medical Institute

**Title:** Analyzing large-scale neural data with Suite2p

**Authors:** \*C. STRINGER<sup>1</sup>, C. KI<sup>2</sup>, P. K. LAFOSSE<sup>3</sup>, Q. ZHANG<sup>4</sup>, N. A. DEL GROSSO<sup>5</sup>, M. PACHITARIU<sup>1</sup>;

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**Abstract:** Two-photon calcium imaging has become a standard technique for recording the activity of thousands of neurons simultaneously, with many labs generating hundreds to thousands of gigabytes of data per day. To process these large datasets, we developed Suite2p, an efficient and accurate pipeline for motion correction, cell detection, trace extraction and spike detection. Most imaging is performed in vivo and thus there is often movement of the field of view, making motion correction crucial. We designed a GPU-accelerated non-rigid motion correction algorithm, which achieves ten times faster processing speeds than previous approaches. This algorithm was optimized for functional imaging and provided more precise alignment than other algorithms when benchmarked on real recordings of visual cortical neurons with an anatomical marker. We developed an algorithm for functional neural segmentation using L0-sparse matrix reconstruction, which is substantially faster than prior approaches. To benchmark cell detection algorithms, we devised a new strategy for producing hybrid ground-truth datasets from real recordings in visual cortex across cortical layers. On these datasets, Suite2p outperformed other cell detection algorithms, finding more cells and producing fewer false positives.

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## Poster

### PSTR223: Visual Cortex: Population Recording and Analysis

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**Program #/Poster #:** PSTR223.06/O11

**Topic:** E.06. Vision

**Support:** NSF IIS-2113197

**Title:** Functional mapping of neurons in primary visual cortex using computational barcodes

**Authors:** \*I. FERNANDEZ<sup>1</sup>, J. ANTOLIK<sup>2</sup>, D. A. BUTTS<sup>3</sup>;

<sup>1</sup>Univ. of Maryland, College Park, MD; <sup>2</sup>Fac. of Mathematics and Physics, KSVI, Charles Univ., Prague, Czech Republic; <sup>3</sup>Dept. of Biol., Univ. of Maryland, Col. Park, College Park, MD

**Abstract:** Visual perception relies on a hierarchy of visual processing that transforms raw visual input into meaningful representations. A fundamental question we address here is how to

understand the contribution of individual neurons in the visual system to this process. Traditionally, functional descriptions of visual neurons have been based on the visual feature(s) that the neuron best responds to, typically summarized by tuning curves or receptive fields. However, such characterizations of neural function can be limiting in more natural visual contexts, where receptive-field-based models often struggle to effectively predict neuron responses, even for neurons at the earliest cortical stage of processing: the primary visual cortex (V1). Recently, models based on deep neural networks (DNN) have been shown to better predict V1 responses and likewise provide a more faithful representation of their role in visual processing. However, they lack the ability to provide an interpretable description of a given neuron's function, due to their depth and complexity. Here we present a variant of a DNN-based model that provides an interpretable framework based on the concept of *computational barcodes*, which are unique identifiers of each neuron based on the computation that it performs; such that computational barcodes of neurons with the same computational role in visual processing will have the same barcode, and likewise, neurons that share computations (e.g., within a neural circuit) will have similar barcodes. To isolate these functional representations, we structure the DNN to be convolutionally invariant for spatial position and orientation, ensuring that the same computations are identified in neurons with different spatial positions and orientations. To evaluate this approach, we used synthetic data produced by a large-scale spiking neural network model of V1 with biologically realistic connectivity and cell types that can reproduce many known classical and extra-classical properties. We show that this barcode approach can distinguish different cell types (layer 4 versus 2/3, excitatory versus inhibitory) based on unsupervised clustering in a "barcode space". We further validate this framework using macaque V1 recording. We propose computational barcodes as a new alternative to feature-based descriptions of neural function that can be used to understand visual neuron function at a population level over hierarchical visual computations. This approach provides a path towards a comprehensive understanding of the architecture of the visual cortex directly tied to visual function in natural visual contexts.

**Disclosures:** I. Fernandez: None. J. Antolik: None. D.A. Butts: None.

## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.07/O12

**Topic:** E.06. Vision

**Title:** An information-theoretical approach to optimize task design for distinguishing probabilistic codes in neural populations

**Authors:** \*P.-C. KUO, E. Y. WALKER;  
Neurobio. and Biophysics, Univ. of Washington, Seattle, WA

**Abstract:** Bayesian inference provides a powerful framework for understanding the neural computation underlying perception and perceptual decision-making. Two competing theories have been proposed for how neural populations may encode probabilistic sensory information: probabilistic population codes (PPC) that encode the likelihood functions  $p(r|\Theta)$  and neural sampling codes (NSC) that encode the posterior distributions  $p(\Theta|r)$  over stimuli. The critical distinction lies in whether stimulus priors would modulate neural population responses in early sensory areas. However, distinguishing the two codes experimentally has been challenging as it is unclear what stimulus distributions would maximally differentiate populations that follow likelihood and posterior codes. We developed an information-theoretical approach to optimize task design for distinguishing these probabilistic representations. Our method derives an expected difference measure in decodable information when applying likelihood versus posterior decoders, implemented using deep neural networks. We show this expected difference can be evaluated as the information gap when decoding mismatched probabilistic quantities, specifically the KL divergence between the true posterior and a posterior marginalized over surrogate stimulus distributions:  $\Delta^* = D_{\text{KL}}(p(\Theta|r) \parallel \hat{p}(\Theta|r))$ . This measure quantifies how effectively a given task design can differentiate between likelihood and posterior codes. We validate the proposed expected information gap approach on simulated likelihood-coding and posterior-coding populations. Critically, maximizing this expected information gap yields stimulus distributions that maximally differentiate between the two probabilistic codes. Our information-theoretical approach provides a principled framework for designing targeted experiments to identify the underlying probabilistic neural code, advancing our understanding of how neural populations represent uncertainty and make perceptual decisions under Bayesian inference principles.

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**Poster**

**PSTR223: Visual Cortex: Population Recording and Analysis**

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**Program #/Poster #:** PSTR223.08/O13

**Topic:** E.06. Vision

**Support:** SPRING JPMJSP2157

**Title:** Decoding visual information from low-dimensional ecog data in mouse visual cortex

**Authors:** \*S. YAMADA, H. ITO;  
Kyoto Sangyo Univ., Kyoto, Japan

**Abstract:** Brain-machine interfaces (BMIs) have advanced dramatically, provided by improving multiple sites electrode and statistical analysis. However, most high-performance devices are highly invasive, making their long-term use difficult. In addition, higher dimensionality of neural data has caused data analysis to be more difficult. To address these issues, we recorded low-



dimensional neural data (LFPs: Local field potentials) by ECoG electrodes and attempted to extract visual information using various machine learning models. ECoG electrodes ( $2 \times 3$ ) made of biocompatible materials were implanted on the mouse visual cortex (five mice), and we presented four different visual stimuli (white horizontal rectangle at the top, center, and bottom stimuli on the display, and no stimulus) monocularly under anesthesia (Isoflurane). The visual evoked potentials were observed within 1.0 sec after the stimulus presentation. To decode on the presented visual stimuli, discrimination models were constructed with the Convolutional Neural Network (CNN). This model was trained with 80% of the whole LFPs data (1.0 sec duration, 6 channels, 500 trials/day for each stimulus, 10 days) and cross-validated the discrimination accuracies with the other 20% of the data. We found that the discrimination accuracies (45 ~ 65%) were significantly higher than chance level (25%) for all mice, confirming that the information on the stimulus locations can be extracted even from low-spatial-resolution ECoG signals. Next, we examined which features of the spatio-temporal data contain the stimulus information. A new dataset was created by deleting (dropping) 0.1 sec intervals from the original data (1.0 sec, 6 channels), and the model was evaluated using each of the 10 types of datasets associated with the deleted interval. The discrimination accuracies were significantly declined by the droppings from 0.0 to 0.2 sec after the stimulus presentation. To identify the number of necessary dimensions for the decoding, we tested the dimensionality-reduced data using various machine learning models (SVM, LDA, K-Means and Logistic-regression). The results showed that all models were able to discriminate visual stimuli with approximately 200-300 dimensions of information (the dimension of the original data is 720). Our research results suggest that quantification and feature analysis of visual information by machine learning models is feasible even to low-dimensional ECoG data.

**Disclosures:** S. Yamada: None. H. Ito: None.

## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

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**Program #/Poster #:** PSTR223.09/O14

**Topic:** E.06. Vision

**Support:** KAKENHI JP(21K19803)  
Kyoto Sangyo Univ. Research Grant (M2301)

**Title:** Nonlinear decoder is necessary for decoding of neuron population with stimulus dependent spike count correlations

**Authors:** \*H. ITO<sup>1</sup>, Y. TABATA<sup>1</sup>, R. KOHNO<sup>1</sup>, Y. MARUYAMA<sup>2</sup>, Y. MORI<sup>3</sup>;

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**Abstract:** There were several reports suggesting the importance of finite spike count correlations for information decoding by the neuron populations. However, most studies adopted linear decoders or the linear Fisher information. We recorded multiple single neurons in the visual cortex of anesthetized cats under the moving bar of 16 different directions. We have shown that the variabilities were correlated between the neuron pairs (spike count correlation) and some neuron pairs showed stimulus dependent spike count correlations (Maruyama & Ito, 2013). Our main interest is how the spike count correlations and their stimulus dependence contribute to the decoding performance of the stimulus directions. We applied the non-linear Support Vector Machine (SVM) model with the RBF kernel and selected the hyper parameters to optimize the performance of the cross-validation. At first, we found that the original data with finite spike count correlations showed higher discrimination accuracy than the data without correlation (independent variabilities) obtained by the trial shuffling ( $P < 0.005$ ,  $N = 30$ ). Examining the contribution of stimulus dependent spike count correlation, we introduced a novel stimulus shuffling method by which unit pairs in all the stimulus clusters had the identical but finite spike count correlation averaged over all the stimuli. The original data with stimulus dependent spike count correlations showed higher discrimination accuracy than the stimulus shuffled data ( $P < 0.026$ ,  $N = 30$ ). For each neuron population, the degree of stimulus dependent variations of the spike count correlations was quantified by averaging the test statistic H-value of the Kruskal-Wallis test over all the unit pairs. We also estimated the ratio of the increase in the discrimination accuracy of the original data compared with the stimulus shuffled data. We found that the ratio of the increase in the discrimination accuracy showed a significant positive correlation to the degree of stimulus dependent variations of the spike count correlations ( $r = 0.51$ ,  $P < 0.004$ ,  $N = 30$ ). Neuron populations with larger stimulus dependent variations of the spike count correlations tended to have larger increase ratios in the discrimination accuracy. Finally, non-linearity was essential since the non-linear SVM showed higher discrimination accuracy than the linear SVM ( $P < 0.001$ ,  $N = 25$ ). The linear SVM showed lower discrimination accuracy than the non-linear SVM of the stimulus shuffled data and comparable accuracy to the non-linear SVM of the trial shuffled data. Those results suggest that the nonlinear decoder is essential for decoding the neuron population with the spike count correlations.

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## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

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**Program #/Poster #:** PSTR223.10/O15

**Topic:** E.06. Vision

**Title:** Single-unit activity in visual cortex of the sedated and anesthetized brain

**Authors:** \*D. L. MIKULEK<sup>1</sup>, A. R. ANDREI<sup>1</sup>, A. G. MCCONNELL<sup>1,2</sup>, S. EGRANOV<sup>1,2</sup>, V. DRAGOI<sup>3,1,4,5</sup>;

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**Abstract:** Anesthetics greatly affect the large-scale rhythms of the brain. In clinical settings, this is often monitored via electro-encephalograms (EEGs), but the effects on populations of individual cortical neurons have not been extensively explored. Further, certain anesthetics are commonly used for euthanasia in both animals and humans, so understanding the time-course and nature of effects on individual neurons is critical. Recently, studies in both rodents and humans found that the mammalian brain can generate a paradoxically heightened state of electrical activity through a surge of gamma power, connectivity, and coupling after the heart stops. Here we report the first single-unit activity recorded in nonhuman primates during sequential administration of anesthetics commonly used in clinical practice. We performed EEG, EKG, and multielectrode extracellular recordings in the visual cortex of two male rhesus macaques. We administered ketamine for sedation, followed by isoflurane and pentobarbital in one macaque, while the other received additional doses of propofol, midazolam, and phenytoin. Thus far, the data show a significant decrease in firing rate after each anesthetic with the firing rate 30s after pentobarbital being indistinguishable from firing rate after the heart stopped. We also found a brief surge in local field potential (LFP) gamma power (40-100 Hz) following the cessation of a cardiac signal, as well as a late burst of activity across multiple frequencies nearly 300 seconds afterwards. Further examination of this neural data will reveal cortical population dynamics with precise temporal and spatial resolution of unmatched quality. Furthermore, the data gathered from this procedure will inform neural monitoring devices and treatment for patients who are at risk of death or are in a comatose state.

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## **Poster**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.11/O16

**Topic:** E.06. Vision

**Support:** STI2030-2022ZD0204600

**Title:** Feature orthogonality in the population response of macaque V1

**Authors:** \*X. WANG<sup>1</sup>, S. ZHANG<sup>2</sup>, S. TANG<sup>3</sup>, C. YU<sup>3</sup>;

<sup>1</sup>peking university, peking, China; <sup>2</sup>Peking-Tsinghua Ctr. for Life Sci., Peking Univ., Beijing City, China; <sup>3</sup>Peking Univ., Beijing, China

**Abstract:** The classical ice-cube model of Hubel and Wiesel proposes that V1 neurons are spatially organized into orthogonal maps of orientation and ocular dominance to optimize wiring efficiency. However, extending this model to incorporate additional features such as spatial frequency imposes geometric constraints on the two-dimensional cortical surface. Our recent two-photon calcium imaging study in awake macaques revealed that cellular-resolution maps of orientation, spatial frequency, and ocular dominance do not consistently exhibit orthogonal or parallel arrangements (Zhang et al., 2024), challenging traditional map-based frameworks. In this study, we investigated whether these independent features can nevertheless be orthogonally represented in population response patterns. We applied multidimensional scaling (MDS) to simultaneously recorded responses of over 1000 neurons per FOV in four macaques. Despite the absence of consistent orthogonal or parallel intersections among cortical maps of orientation, spatial frequency, and ocular dominance, these features were encoded along near-orthogonal axes in a three-dimensional representational space, with mean intersection angles of  $81.06^\circ \pm 2.34^\circ$  (ORI-OD),  $76.04^\circ \pm 5.34^\circ$  (ORI-SF), and  $80.84^\circ \pm 2.46^\circ$  (SF-OD). These findings support a population-based, rather than anatomically constrained, encoding strategy. Consistent with previous reports, only a small fraction ( $5.82\% \pm 1.36\%$ ) of neurons were tuned to low spatial frequencies below 1 cpd. Nonetheless, the population exhibited robust and well-differentiated responses to low-frequency information. These responses were reliably separable in MDS space, as quantified by a silhouette coefficient index (SCI) of  $0.19 \pm 0.07$ , significantly exceeding shuffled controls ( $-0.08 \pm 0.01$ ). Pairwise classification using linear SVMs further confirmed discriminability, with accuracies of  $87.08\% \pm 6.67\%$  (0.25 vs. 0.5 cpd),  $90.00\% \pm 3.45\%$  (0.5 vs. 1 cpd), and  $97.92\% \pm 1.61\%$  (0.25 vs. 1 cpd). In conclusion, these results reveal a latent orthogonal structure in V1's representational geometry among multiple stimulus features and highlight the need to shift from spatially organized cortical maps toward distributed, high-dimensional population codes as the organizing principle of early visual processing.

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## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

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**Topic:** E.06. Vision

**Support:** STI2030-Major Projects, grant no. 2022ZD0204600  
National Natural Science Foundation of China, grant no. U1909205

**Title:** Multi-modal coding of natural scenes revealed by a massive single-neuron dataset in primate anterior inferotemporal cortex

**Authors:** \*Q. LU<sup>1</sup>, X. XIONG<sup>2</sup>, S. TANG<sup>2,4,5,3</sup>;

<sup>2</sup>Sch. of Life Sci., <sup>3</sup>Key Lab. of Machine Perception (Ministry of Education), <sup>1</sup>Peking Univ.,

Beijing, China; <sup>4</sup>Peking-Tsinghua Ctr. for Life Sci., Beijing, China; <sup>5</sup>IDG/McGovern Inst. for Brain Res. at Peking Univ., Beijing, China

**Abstract:** The inferotemporal (IT) cortex is widely recognized as a critical brain region for object recognition in primates. Nevertheless, the neural coding of natural scene in anterior inferotemporal (AIT) cortex remains unclear. Using Neuropixels 2.0, we collected a massive single-neuron dataset from macaque AIT, which includes hundreds of single-neuron responses to thousands of natural images. We found that the response sparseness and selectivity of AIT neurons exhibit a broad distribution. Non-sparse neurons responsive to 10%-2% of presented images encoded elementary visual features including textures, simple shapes and coarse object category (e.g., faces). Neurons with intermediate response sparseness responded to 2%-0.5% of images, representing various moderately complex features and combination of features (e.g., faces with a horizontal line). Highly sparse neurons have been found responsive to a few distinct images. We also found a subset of neurons responding extremely sparsely to 1-2 images among thousands presented. These results suggest that primate AIT employs a multi-modal coding scheme to facilitate efficient and precise object recognition.

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## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

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**Topic:** E.06. Vision

**Support:** Wellcome Trust-DBT India Alliance (Grant number: IA/S/18/2/504003)  
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**Title:** Stimulus contrast and size differentially shift the drift-rate tuning of gamma oscillations in macaque primary visual cortex

**Authors:** \*S. S. PRAKASH, S. RAY;  
Ctr. for Neurosci., Indian Inst. of Sci., Bangalore, India

**Abstract:** Gamma oscillations are thought to emerge from excitation-inhibition (E-I) interactions, yet the precise dependency of gamma power on E-I balance remains unclear. This relationship is of particular interest due to alterations in gamma responses observed in clinical populations with suspected E-I imbalances, such as autism and premenstrual dysphoric disorder. Increasing the drift-rate of the visual grating, which changes E-I balance, increases the peak frequency of gamma, while the peak power initially increases and later attenuates. Prior MEG work in humans (Orekhova et al., 2020) demonstrated that increasing stimulus contrast reduces the preferred drift-rate of gamma oscillations (i.e., a leftward shift in the drift-rate vs. gamma power curve), suggesting that excess excitation may recruit stronger inhibition, attenuating gamma power at high input strengths. To further examine the effect of excitatory and inhibitory

drive on gamma oscillations, we recorded local field potentials using 48-channel Utah arrays from the primary visual cortex (V1) of two bonnet macaques (*Macaca radiata*; 1 female, 1 male), while we presented grating stimuli of varying contrast and size, drifting at a range of temporal frequencies (drift-rates), during the passive fixation task. Since contrast modulates both excitatory and inhibitory drive, while size primarily recruits surround suppression, we hypothesized that these manipulations would differentially shift the gamma tuning curve. As predicted, increasing contrast induced a leftward shift in the drift-rate tuning of gamma power, consistent with earlier human studies, whereas increasing size caused a rightward shift. These findings suggest that gamma oscillations could reflect an optimal E-I balance in cortical circuits and underscore their potential use as biomarkers for neuropsychiatric conditions involving E-I dysregulation.

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## **Poster**

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**Program #/Poster #:** PSTR223.14/P3

**Topic:** E.06. Vision

**Support:** NSF GRFP 2146755  
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Howard Hughes Medical Institute

**Title:** Modularity of pattern motion selectivity within visual area MT of the macaque

**Authors:** \*E. TREPKA<sup>1</sup>, C. YUE<sup>2</sup>, R. XIA<sup>2</sup>, S. ZHU<sup>2</sup>, S. SALEKI<sup>2</sup>, T. MOORE<sup>2</sup>;  
<sup>1</sup>Neurosciences Interdepartmental Program, Stanford Univ., Menlo Park, CA; <sup>2</sup>Neurobio., Stanford Univ. & Howard Hughes Med. Inst., Stanford, CA

**Abstract:** Neurons in the macaque middle temporal visual area (MT) are generally selective to the direction of visual motion and many are also selective to the motion of complex patterns, independent of the orientation of their components. To study the functional organization of pattern direction selectivity, we recorded the activity of large populations of single neurons from area MT using Neuropixels NHP 1.0 probes in two male Rhesus macaques. Each recording utilized a single bank of the Neuropixels probe, spanning ~4 mm of cortex. We probed neurons with either drifting gratings or plaids composed of two gratings with orientations offset by 120°. We then classified neurons as pattern direction selective (PDS) or component direction selective (CDS) based on the correlation between the observed responses to plaids and the responses predicted by the canonical PDS and CDS models. Across recording sessions in both monkeys, we found that PDS and CDS cells were not randomly intermixed along the length of the recording electrode. Rather, we observed modularity in the organization of PDS and CDS cells, with clusters of each cell type extending up to 500 µm. Our results demonstrate a modular

organization of pattern direction selectivity in area MT, with implications for how such selectivity arises in visual cortex.

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.15/P4

**Topic:** E.06. Vision

**Support:** STI2030-Major Projects (2022ZD0208200)

**Title:** Teo neurons represent figure-ground signal through a push-pull response pattern

**Authors:** \*S. WANG<sup>1</sup>, R. GUO<sup>1</sup>, W. LI<sup>2</sup>, Y. YAN<sup>3</sup>;

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**Abstract:** TEO neurons represent figure-ground signal through a push-pull response pattern **Authors** Surigui Wang<sup>1,3</sup>, Ruining Guo<sup>1,3</sup>, Wu Li<sup>1,\*</sup>, Yin Yan<sup>1,2,\*</sup>; <sup>1</sup> State Key

Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, China;<sup>2</sup> Chinese Institute for Brain Research, Beijing, China; <sup>3</sup> These authors contributed equally. \*Corresponding author **Abstract** Separating task-relevant foreground objects from cluttered backgrounds is essential to visual processing. Prior research shows that figure-ground segmentation progresses along the visual cortical hierarchy, from V1 to V4. Since V4 projects to decision-related areas like the frontal eye fields (FEF) and prefrontal cortex (PFC), it can directly support behavioral responses. However, whether this information is further processed or explicitly represented in downstream higher-order areas like the temporal-occipital (TEO) cortex remains unclear. To investigate, we implanted multi-electrode arrays into the TEO cortex of macaque monkeys and recorded neuronal responses to figure-ground stimuli defined by oriented textures or collinear contours. In texture-defined figures, full-screen textures of uniformly oriented lines contained a rectangular figure formed by rotating line orientation within the figure region by 90°. In contour-defined figures, short bars were randomly oriented, with subsets aligned to form collinear contours; contour saliency increased with the number of aligned bars. TEO neurons exhibited a distinctive push-pull coding pattern for figure-ground signals. One population (“push” neurons) increased firing with higher figure saliency, while another (“pull” neurons) decreased firing. This push-pull organization was consistent across both figure types and invariant to figure orientation (e.g., 45° or 135°), suggesting a general TEO coding strategy rather than stimulus-specific responses. The decreased activity in pull neurons could not be explained by receptive field overlap with background regions, as response profiles remained consistent when the figure was spatially

shifted, indicating spatial invariance. Additionally, push and pull neurons were spatially clustered on the cortical surface. In summary, TEO neurons encode figure-ground relationships via a push-pull strategy, with complementary neuronal populations responding oppositely to figure saliency. This architecture may drive differential feedback to earlier visual areas, modulating visual information flow based on figure-ground context. **Keywords:** temporal-occipital cortex; figure-ground segregation; push-pull coding

**Disclosures:** S. Wang: None. R. guo: None. W. Li: None. Y. Yan: None.

## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.16/P5

**Topic:** E.06. Vision

**Support:** NIH R01EY23384

**Title:** Taking Saccade Timing Into Account Improves Encoding Models of Visual iEEG Responses

**Authors:** \*M. N. MONTOYA<sup>1</sup>, Z. QADIR<sup>2</sup>, H. HUANG<sup>1</sup>, G. OJEDA VALENCIA<sup>1</sup>, G. A. WORRELL<sup>2</sup>, K. J. MILLER<sup>3</sup>, T. NASELARIS<sup>4</sup>, K. N. KAY<sup>5</sup>, D. HERMES<sup>1</sup>;

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**Abstract:** Natural scene images are filled with compelling details that may draw our eyes to regions of interest. However, experimental designs often require central fixation in order to simplify the estimation of models of stimulus-evoked brain activity. Due to the interesting content in images, some subjects will, however, still make saccadic eye movements during fixation tasks. Therefore, we test how saccades impact the accuracy of visual encoding models that predict neural activity in an experiment where subjects were required to fixate but sometimes made erroneous saccades. We measured high-frequency broadband (70-170Hz) responses from 19 V1-V3 electrodes across eight subjects (18-40 years old, 5 females) who were implanted with stereotactic EEG (sEEG) electrodes for clinical purposes. Eye tracking data were simultaneously measured while subjects were instructed to fixate during 1000 select images from the Natural Scenes Dataset (NSD) and tested on recognition of shown images vs. distractors after each run. Images were shown 800 ms on, 800 ms off, and were displayed in 10 separate runs recorded over multiple days. Out of the 1000 unique images, 100 were repeated six times and 900 images were shown once. The eye tracking data showed that across all 8 participants, very few eye movements were made between 50-100 ms after image onset and most eye movements occurred after 200 ms. Given the relative absence of eye movements between 50-100 ms, we trained a visual encoding model (the Second-Order Contrast (SOC) model) on broadband data from 50-100 ms from all repeated images. The model provided accurate pRF estimates across



electrodes. We then tested how well the model predicted activity for the left out non-repeated images across time. The model predicted neural activity well for trials where subjects were fixating, explaining ~85% of variance around 100 ms after image onset. Model prediction declined after ~170 ms, in line with the decrease in broadband signal amplitude. A similar prediction pattern was observed for trials with saccades. However, around 200 ms, the model explained ~5% more variance in trials with central fixation compared to trials with saccades. Furthermore, a model trained on broadband data from 150-200 ms performed worse compared to the model trained on data from 50-100 ms. These results indicate that reliable visual encoding models can be built on data from time windows unaffected by saccades. Eye tracking can help inform the timing of saccades and provide a unique perspective on how we can improve models of vision by taking eye movements into account.

**Disclosures:** M.N. Montoya: None. Z. Qadir: None. H. Huang: None. G. Ojeda Valencia: None. G.A. Worrell: None. K.J. Miller: None. T. Naselaris: None. K.N. Kay: None. D. Hermes: None.

## **Poster**

### **PSTR223: Visual Cortex: Population Recording and Analysis**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR223.17/P6

**Topic:** E.06. Vision

**Support:** BMBF Grant 01GQ2101

**Title:** Human Visual Population Receptive Field Mapping at an Ultra-High Field Strength of 9.4 T and Submillimeter Resolution

**Authors:** \*D. RAMADAN<sup>1</sup>, S. STOLL<sup>1,2,3</sup>, P. R. GRASSI<sup>4,1,5</sup>, S. MUELLER<sup>1</sup>, V. JANGIR<sup>1</sup>, K. SCHEFFLER<sup>1,6</sup>, J. BAUSE<sup>1</sup>;

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**Abstract:** At ultra-high field (UHF) strengths ( $\geq 7$ T), functional magnetic resonance imaging (fMRI) at submillimeter resolution becomes feasible in the human brain. This allows for the quantification of intricate functional signatures across cortical depths, such as visual population receptive fields (pRFs). However, smaller voxel sizes result in longer repetition times (TRs), and thus longer run durations, which increases participant demands and reduces the amount of data collected per scanning session. This poses challenges for visual pRF mapping, as a single mapping stimulus typically traverses the visual field in increments of TR. Moreover, the scanning sequence predominantly used at UHF - gradient echo echo-planar imaging (GRE-EPI) -

suffers from a bias towards large draining veins, which might distort pRFs. Here, we therefore compared two time-efficient pRF mapping designs using an alternative scanning sequence called balanced steady-state free precession (bSSFP), which is considered less prone to macrovascular biases. For both designs, we used standard bar stimuli that traversed the visual field step-by-step along cardinal and oblique axes interspersed with rest periods. In the 2-bar design, we increased efficiency by having 2 bar stimuli (instead of 1). In the 1-bar-smooth design, we achieved this by using a single bar stimulus that moved smoothly in sub-TR increments. We scanned one participant at 9.4 T and collected 4 runs of equal length (10 min 14 s) per design capturing the occipital cortex with a nominal resolution of  $(0.8 \text{ mm})^3$  and a TR of 4206 ms. To estimate pRF position and size, we fitted a 2D Gaussian pRF model to the data. The resulting pRF position and size maps for the 2-bar design were more complete and continuous compared to the 1-bar-smooth design, possibly due to the use of sub-TR increments or multiple bars. For both designs, the pRF position maps revealed typical retinotopic signatures, such as a mapping of the central-to-peripheral visual field onto a posterior-to-anterior axis in the occipital cortex. In contrast, the pRF size maps revealed smaller pRFs for the 2-bar design and no clear pRF size gradient for either design. Our results demonstrate the general feasibility of visual pRF mapping at 9.4 T and submillimeter resolution with bSSFP and more efficient designs, whilst highlighting a potential superiority of the 2-bar design and challenges when it comes to quantifying pRF sizes. These findings lay the foundation for subsequent comparisons between bSSFP and the more common GRE-EPI, as well as depth-dependent pRF quantifications.

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## **Poster**

### **PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.01/P7

**Topic:** E.06. Vision

**Support:** Max Planck Society  
The Boehringer Ingelheim Fonds PhD fellowship

**Title:** Longitudinal imaging tracks single-neuron correlates of visual category learning in mouse lateral visual cortex

**Authors:** \*J. KLOS, T. BONHOEFFER, M. HUEBENER, P. M. GOLTSTEIN;  
Max Planck Inst. for Biol. Intelligence, Martinsried, Germany

**Abstract:** Our brains constantly categorize to make sense of our world. The neural implementation of this process very likely depends on the formation of category-selective neurons, which, after learning, have been observed throughout the brain, including lateral visual cortex (Freedman and Assad, 2016). However, the exact neuronal signals and plasticity

mechanisms required for neurons to acquire such selectivity remain unknown. Theoretical work indicates a role for local reward and choice signals in gating the stimulus dependent plasticity that results in category tuning (Engel et al., 2015). Here, we provide more insight into this mechanism by tracking the development of neuronal correlates of category, choice, reward and other related factors in the lateral visual cortex of mice learning a visual categorization task. We defined visual categories by diagonally dividing a two-dimensional stimulus space consisting of 30 drifting gratings varying in orientation and spatial frequency. Using a two-alternative choice paradigm (lick left/lick right), we first trained head-fixed mice (n=10) to discriminate two stimuli, one from each category, differing only in orientation. On subsequent blocks of sessions, we added additional stimuli that were progressively closer to the category boundary until the task consisted of the full stimulus set. Throughout stimulus discrimination and category learning stages, we performed repeated two-photon calcium imaging, recording the activity of the same lateral visual cortex neurons while mice performed the task. In addition, we obtained high-resolution video data tracking multiple views of the body and eyes. Three mice learned the full categories, four showed intermediate (variable) performance and three failed to learn the initial discrimination task. Analysis revealed that poor performance correlated with non-optimal behavioral strategies such as basing choices on recent trial outcomes or preferring a single lick spout altogether. We tracked the activity of 471 ( $\pm 156$  s.d.) neurons per mouse over six consecutive in-task sessions spanning the category learning stages, and two passive viewing sessions - at the beginning and end of the experiment. During task performance, we found single-neuron correlates for key task-, and learning-related variables like category, choice, reward and error, alongside tuning for stimulus features (orientation and spatial frequency) and behavioral states. We are currently exploring how these neural correlates dynamically reorganize at the population level, and how these changes relate to the diverse behavioral learning trajectories.

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## **Poster**

### **PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.02/P8

**Topic:** E.06. Vision

**Title:** The effect of real world experience on short- and long-term memory for everyday objects

**Authors:** \*S. C. WAYMER<sup>1</sup>, S. G. WARDLE<sup>2</sup>, C. I. BAKER<sup>3</sup>;

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**Abstract:** Every day we physically interact with many objects (e.g. using keys to open a door, writing a note with a pen), but how well can we remember specific details about the objects we encounter? Most research on visual memory is conducted on words and images using computer-based tasks, but it's possible that the process of interacting with real-world objects influences

memory. Here we examine short- and long-term recall and recognition memory for everyday objects (e.g. mug, shoe, clock) as a function of the type of real-world experience (haptic exploration vs. visual exploration). Participants ( $N = 40$ ) explored 24 objects for 30 seconds each, in random order. Participants in the haptic exploration group ( $n = 20$ ) held and manually explored the objects, while participants in the visual exploration group ( $n = 20$ ) viewed the objects on a turntable from a distance and controlled the rotation speed and direction using a mobile phone. Participants were videorecorded during both exploration and memory phases. Following a brief distractor task (digit span), participants were asked to freely recall the objects they had explored providing as much detail as possible. Additional recall was encouraged using planned category prompts (e.g. Do you remember any clothing?) and two foils as catch trials (e.g. Do you remember any kitchen utensils?). This was followed by a computer-based recognition task containing 72 images of the explored objects in three orientations and 72 images of similar unexplored objects. Eighteen participants returned 2 months ( $\pm 2$  weeks) later for an unexpected follow-up to repeat the recall and recognition tasks. Following exploration of real-world objects, about 2/3 of the objects were remembered during immediate free recall, regardless of the type of exploration (haptic vs. visual-only). However, haptic exploration led to significantly better discrimination performance ( $d'$ ) on the short-term visual recognition task ( $p < .05$ ). During recall some objects were remembered more often than others, with a recall advantage for thematically linked objects (e.g. sneaker, heel) over distinctive items (mask, birdhouse). At the 2-month follow-up, we observed substantial long-term recall and recognition memory for the explored objects, yet some participants also generated false memories of objects that were never explored (e.g. doll). In addition to false memories, there were more inaccuracies in the details of the recalled objects after two months (e.g. combining the identity of one object with the visual characteristics of a second object). Together, our results reveal new insight into how visual memory is influenced by real-world experience.

**Disclosures:** S.C. Waymer: None. S.G. Wardle: None. C.I. Baker: None.

## **Poster**

### **PSTR224: Visual Learning, Memory, and Categorization**

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**Program #/Poster #:** PSTR224.03/P9

**Topic:** E.06. Vision

**Support:** NIH R01EY032878  
Simons Collaboration on the Global Brain 543033

**Title:** Resolving a paradox about how vision is transformed into recognition memory

**Authors:** \*S. BOHN, C. M. HACKER, B. G. JANNUZI, T. MEYER, M. L. HAY, N. C. RUST;  
Psychology, Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** While humans and other primates can generally remember whether they've seen images before with remarkable capacity and detail, specific images are systematically more likely to be remembered or forgotten. Here, we use this behavioral signature, 'image memorability', to unravel a paradox about how the brain stores and signals visual recognition memories. The paradox results from two seemingly contradictory observations: (1) the characteristic reduction in firing to a repeated image, repetition suppression (RS), in inferotemporal cortex (ITC) generally aligns well with memory behavior and is thought to signal memory. However (2), in ITC, more memorable images evoke greater firing rates than less memorable ones. If *reduced* firing signals memory, why are images that evoke *greater* firing more likely to be remembered?

We hypothesized that ITC memory representations are transformed by downstream computations in the medial temporal lobe such that firing rates in the hippocampus (HC) can be read out to signal memory. To test this, we recorded and compared neural activity in ITC and HC as two rhesus macaque monkeys performed a visual recognition memory task. We found evidence consistent with the predictions of this hypothesis: memorability modulation was greatly attenuated in HC, but modulation by memory remained. Furthermore, RS remained larger for more memorable images in HC, consistent with the prediction that RS drives memorability behavior.

Next, we explored models that might account for this medial temporal lobe transformation. Simple accounts, like a late window- or thresholded-readout on the ITC population, could not produce the representations in HC. However, a linear decoding scheme applied to ITC that sought to preserve memory while eliminating memorability modulation aligned with memorability behavior. This demonstrates that all the information required to form the representations observed in HC is present within ITC and is broadly consistent with a feedforward understanding of visual memory storage and signaling.

Taken together, these results suggest a model of visual memory where more memorable images evoke greater population firing in ITC, leading to more RS. Next, computations in the medial temporal lobe extract firing rate modulations due to memory while eliminating other sources, leaving an isolated memory representation reflected in HC population firing. These results resolve the paradox of memorability in ITC and suggest a new role for the medial temporal lobe in visual recognition memory.

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## **Poster**

### **PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.04/P10

**Topic:** E.06. Vision

**Support:** NIH Grant 5T32NS095939-09  
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**Title:** Incorporating priors into a vector-symbolic model of scene understanding: inference via factorization in a probabilistic generative model for visual scenes

**Authors:** \*K. HUCH<sup>1</sup>, F. T. SOMMER<sup>2</sup>;

<sup>1</sup>Univ. of California, Berkeley, Berkeley, CA; <sup>2</sup>Univ. California, Helen Wills Neurosci Inst., Helen Wills Neurosci. Institute, UC Berkeley, Los Angeles, CA

**Abstract:** In a recent model of visual scene perception [1], scene understanding is accomplished by inverting a generative model of visual scenes employing the framework of vector-symbolic architecture (VSA) [2]. VSAs encode object attributes by distributed representations (population vectors) and offer two different dyadic vector operations, one for binding different attributes to an object, such as pose and object identity, and the other for composing different objects into a scene. Scene understanding then involves the factorization of an individual object representation into its component attributes (i.e., color, shape, location). The factorization of composite vector representation into a product of valid code vectors of object attributes is a long-standing problem in the VSA literature, and the recent study proposes a novel architecture, resonator networks, for solving it. Specifically, a resonator network combines attractor networks, each memorizing the code vectors for one attribute, and a vector binding circuit, to iteratively refine the estimation of all object attributes to ultimately maximize the similarity between the model's internal representation of the scene and the actual input scene. Here we introduce a probabilistic framework for resonator networks, enabling the use of statistical priors over any or all object attributes. In our model, each possible value of a given attribute is assigned a probability representing the expectation that it will appear in the scene. The model's internal representation of a given object in the scene is then refined using a combination of the similarity measurement between the internal representation and the input scene as well as the priors assigned over all possible object attribute values. The new model can thus capture learned scene statistics or expectations for values of specific object attributes. Additionally, it enables sub-linear search for finding objects with a given attribute value in a crowded scene; a massive improvement over the previous model in which every object had to be individually classified before specific objects could be identified.

[1] Renner, A., Supic, L., Danieleescu, A. et al. Neuromorphic visual scene understanding with resonator networks. Nat Mach Intell 6, 641-652 (2024). <https://doi.org/10.1038/s42256-024-00848-0>

[2] Plate, Tony A. Holographic Reduced Representation: Distributed representation for cognitive structures. Vol. 150. Stanford: CSLI Publications, 2003.

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**Poster**

**PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.05/P11

**Topic:** E.06. Vision

**Support:** Funded by the Brandenburg University of Technology

**Title:** Decoding confidence during visual category learning: a pilot study on stimulus- vs. response-locked BCI classification

**Authors:** \*L. RABE<sup>1</sup>, M. KLUG<sup>1</sup>, Y. PAN<sup>1</sup>, T. ZANDER<sup>2</sup>;

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**Abstract:** A passive brain-computer interface (pBCI) can adapt a system in real time based on input derived from the brain, tuning the system to the mental state of its user. Although cognitive states like workload and error perception have been examined rather extensively, many others remain largely unexplored. For pBCIs used in education or training, learning protocols that adapt in real-time to the individual's level of confidence might support learners on a more individual level. Category learning posits that prior to learning, objects of the same category, e.g. trees, appear similar until we learn patterns that distinguish them, e.g. firs from spruces. Previous studies using electroencephalography (EEG) have identified distinct event-related potentials (ERPs) that seem to be reflective of category learning. More specifically, occipital N1 and a parietal late-positive component (LPC) were shown to discriminate between pre- and post-learning. However, it remains unclear whether we can train a classifier that indicates if participants have successfully learned the categorization between two stimulus groups and how confident they are in their decision. Therefore, this pilot study investigated stimulus-locked versus response-locked offline classification (N=2, 1 woman, age 29 and 30). Building on previous work, participants viewed three different image sets (two artificial, one realistic), each containing two visually similar categories. With trial-by-trial feedback, they were asked to infer the underlying patterns. EEG was recorded with a 64-channel actiCHamp connected to a LiveAmp amplifier. After re-referencing to average, downsampling to 250Hz, rejecting noisy channels, filtering to 1-40 Hz and cleaning eye artifacts with ICA, epochs of 850ms post stimulus and post response cue were used for classification. An LDA classifier employing a windowed-means approach with a 50 ms moving window and 5-fold cross-validation was trained to separate categories A and B. Trained on post-learning trials (> 80 % correct), it was expected to align with the participants uncertainty on pre-learning trials through reduced accuracy. However, results revealed classification accuracies below the statistical chance level for all stimulus sets and for both onsets even for post-learning trials. Behavioural results indicate that participants mastered the categorization during the first 10% of the trials in each condition - considerably fewer than in previous studies using the same stimuli. In future studies, the experimental design as well as the design of the classifiers should be revisited.

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**Poster**

**PSTR224: Visual Learning, Memory, and Categorization**

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NIH Grant RF1NS121913

**Title:** Neuronal signatures of successful one-shot memory in mid-visual cortex

**Authors:** \*G. F. DIRISIO<sup>1</sup>, C. XUE<sup>1</sup>, M. R. COHEN<sup>2</sup>;  
<sup>1</sup>Dept. of Neurobio., <sup>2</sup>Neurobio., Univ. of Chicago, Chicago, IL

**Abstract:** A large number of studies have demonstrated that some images are more easily remembered than others. The features that make images easier or harder to remember are related to, but distinct from mid-level visual features, such as those processed by area V4. We investigated whether the activity of V4, a mid-level visual cortical area, could explain the success of one shot visual memory. The neuronal process of visual recognition memory is challenging to capture for multiple reasons. First, it happens rapidly, making it difficult to dissociate the aspects of the neural code related to sensory processing from memory. Second, feature dimensionality for natural images is extremely high and will greatly affect responses in visual areas thought to contribute. Third, primates excel at this task, making it hard to pinpoint aspects related to what is necessary for successful memory. To address these challenges, we designed a variant of a classic visual image recognition task that allows us to analyze the neural and behavioral ingredients of memory on individual trials. Monkeys view images that are revealed slowly, one fragment at a time, and are rewarded for reporting whether they have seen the image before or not. This gradual reveal lengthens the decision process, giving us a glimpse of each decision as it is unfolding. The extended decision process makes it possible to associate distinct aspects of the visual stimulus or neural population responses with successful or unsuccessful memory encoding or retrieval. We use natural images with data-verified metrics, such as image labels, memorability scores, and similarity scores, to better understand visual modulations that might be occurring or guiding memory. We record from populations of neurons in visual cortex (mid-level area V4, which encodes stimulus properties that impact visual memory). Our strategy is to evaluate how well multiple neural hypotheses (repetition suppression, sparse coding, consistency of neural responses, pattern completion) in visual cortex relate to behavior. Our results suggest that the consistency of neural responses (calculated via the correlation of the population activity on the first and second image presentation, termed population correlation) and pattern completion, in which the dynamics of neuronal responses are sped up for familiar rather than novel stimuli, in area V4 relate strongly to successful visual memory. These findings have significant implications for efforts to repair or enhance learning and memory in human patients and artificial systems.

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**Poster**

**PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H



**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.07/Q1

**Topic:** E.06. Vision

**Support:** NIH IRP ZIAMH 002032  
KAKENHI 19K12149  
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KAKENHI 22K12189  
KAKENHI 19J40302

**Title:** Enhanced Neural Plasticity in monkey TE Compared to TEO During Learning of a Feature-ambiguous Visual Categorization Task

**Authors:** \*W. WANG<sup>1</sup>, B. LI<sup>2</sup>, N. MATSUMOTO<sup>3</sup>, K. HAYASHI<sup>3</sup>, K. MARTINEZ GOMEZ<sup>1</sup>, Y. SUGASE-MIYAMOTO<sup>4</sup>, R. C. SAUNDERS<sup>5</sup>, B. J. RICHMOND<sup>6</sup>, M. A. ELDRIDGE<sup>7</sup>;  
<sup>1</sup>Natl. Inst. of Mental Hlth., Bethesda, MD; <sup>2</sup>Natl. Inst. of Mental Hlth., NIMH, NIH, Bethesda, MD; <sup>3</sup>AIST, Tsukuba, Japan; <sup>4</sup>AIST, Tsukuba/Ibaraki, Japan; <sup>5</sup>Lab. of Neuropsychology, Natl. Inst. of Mental Health, Natl. Inst., Bethesda, MD; <sup>6</sup>NIMH, Bethesda, MD; <sup>7</sup>Lab. of Neuropsychology, Biosci. Institute, Newcastle Univ., Ponteland, United Kingdom

**Abstract:** Primates rapidly categorize visual stimuli by recognizing shared features across exemplars. Our previous lesion studies identified two subregions of the inferior temporal cortex (IT)—TEO and TE—that contribute to visual categorization to differing extents. To examine the neural plasticity underlying category learning, we simultaneously recorded neuronal activity from TEO and TE using chronically implanted Utah arrays in two monkeys during training on a visual categorization task involving morphed images of cats and dogs. Across learning, TE neurons exhibited marked increases in both category specificity (distinguishing between exemplars of different categories) and category generalization (generalizing across exemplars within the same category), whereas TEO neurons showed little change in either measure. Category representation in TE was enhanced during correct versus error trials. Single-cell analyses revealed that category selectivity in TE strengthened with learning, primarily through enhanced encoding of one category. Together with lesion-based evidence, these results highlight a key role for experience-dependent plasticity in TE in supporting visual category learning.

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**Poster**

**PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.08/Q2

**Topic:** E.06. Vision

**Title:** Train/test behavioral cross-validation reveals neural correlates in mice

**Authors:** \*M. A. NUÑEZ, F. DU, L. ZHONG, C. STRINGER, M. PACHITARIU;  
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**Abstract:** In systems neuroscience, animals are often trained until they saturate the psychometric function, producing stereotypical behaviors. This may obscure important system properties, such as generalization and neural correlates. In this study, we trained and tested mice on visual texture classification problems, where they needed to generalize at test time based on mid-level visual features. After learning, mice consistently discriminated the training stimuli at a high accuracy, while their performance on test stimuli varied systematically across categories. To determine a possible neural basis for this variation, we simultaneously recorded over 50,000 neurons from primary (V1) and higher-order visual areas (HVA). We found that medial HVAs, especially superficial populations, encoded invariant visual features that could be used for generalization. Medial HVAs had much less invariance in dark-reared mice, suggesting that the invariance requires visual experience. Finally, the image-by-image neural representation similarity correlated with behavioral choices on test stimuli but not on training stimuli. Thus, animal behavior on test stimuli is directly related to the neural representation of those stimuli. Our findings establish mice as a viable model for studying higher-level visual invariance, and suggest that train/test behavior cross-validation is required to understand neural computations in sensory brain areas

**Disclosures:** M.A. Nuñez: None. F. Du: None. L. Zhong: None. C. Stringer: None. M. Pachitariu: None.

**Poster**

**PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.09/Q3

**Topic:** E.06. Vision

**Support:** R01AG064067

**Title:** Neural correlates of natural forgetting of a visual recognition memory

**Authors:** \*N. PRITCHETT<sup>1</sup>, S. NIRLA<sup>3</sup>, J. SUBRAMANIAN<sup>2</sup>;  
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**Abstract:** Many long-term memories fade over time. Forgetting of long-term memories has been attributed to natural decay or interference from overlapping or related memories. Here, we test whether the presence of memory associated feature in everyday visual experience contribute to

forgetting of long-term visual recognition memory of a grating stimulus. We first characterize the behavioral time course of forgetting in C57BL/6 mice. Next, we examine whether cortical plasticity induced by repeated experience of grating stimuli differs between primary visual and parietal cortices. Finally, we test whether selectively disrupting the familiarity signature in the parietal cortex accelerates behavioral forgetting, and whether removing shared features in everyday visual experience prevents it.

**Disclosures:** N. Pritchett: None. S. Niraula: None. J. Subramanian: None.

**Poster**

**PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.10/Q4

**Topic:** E.06. Vision

**Title:** Targeting reward associated neuronal ensembles in mice V1 can induce behavior responses

**Authors:** \*S. NAREDDULA<sup>1</sup>, A. A. CHUBYKIN<sup>1</sup>, V. SALDARRIAGA<sup>2</sup>;

<sup>1</sup>Biol. Sci., <sup>2</sup>Purdue Univ., West Lafayette, IN

**Abstract:** Learning and memory encoding have been historically associated with higher cognitive brain regions such as the hippocampus and the prefrontal cortex. However, recent studies show that upstream cortical regions are also capable of such higher order functions. Previously in our lab we have shown that visual familiarity evokes low frequency 4-8 Hz theta oscillations in the mouse visual cortex (V1). These oscillations seem to be a mechanism of memory encoding in V1. This oscillatory activity is further modulated by reward association. Mice that were trained to a Go/No-Go visual discrimination task had slightly modified responses in V1 to the Go stimulus versus the No-Go stimulus, showing different frequencies. In order to understand the neural ensembles that make up the reward modulation circuit in V1, we used TRAP2/Ai32 mice to specifically express channelrhodopsin in neurons active during the Go stimulus. We recorded from mice V1 using optrodes to identify the neurons expressing channelrhodopsin by sending laser pulses (opto-tagged). We were able to identify opto-tagged neurons and observe their activity compared to the other neurons for all stimuli. We were also able to activate the opto-tagged neurons with the previously observed Go stimulus associated frequency, which induced reward behavior in mice, without presenting the Go stimulus. Finally we used immunohistochemistry to identify opto-tagged neurons and compare them with No-Go stimulus activity using cfos staining. Our results give us a new insight into memory encoding in V1 and a potential for enhancing learning by targeted stimulation of cortical ensembles.

**Disclosures:** S. Nareddula: None. A.A. Chubykin: None. V. Saldarriaga: None.

**Poster**

## **PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.11/Q5

**Topic:** E.06. Vision

**Support:** This work was supported by internal research funds from Georgetown University Medical Center to TTL.

**Title:** The facilitatory effects of high-frequency transcranial random noise stimulation over bilateral hMT+ on motion discrimination

**Authors:** \*K. MOON<sup>1</sup>, R. RUHDE<sup>1</sup>, L. BATTELLI<sup>2</sup>, G. EDWARDS<sup>3</sup>, T. T. LIU<sup>1</sup>;  
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**Abstract:** Perceptual learning refers to long-lasting improvements in sensory performance resulting from repeated experience with specific, trained stimuli. These behavioral gains are thought to reflect experience-dependent plasticity in sensory cortical areas and/or enhanced readout mechanisms in higher-order visual areas. While perceptual learning has demonstrated efficacy in improving visual functions such as motion discrimination, traditional training protocols often require weeks or months, limiting feasibility for aging or clinical populations. High-frequency transcranial random noise stimulation (hf-tRNS), a noninvasive brain stimulation technique, has been shown to accelerate perceptual learning when paired with training. Here, we explored whether a rapid, same-day hf-tRNS protocol targeting bilateral human middle temporal complex (hMT+) could enhance motion discrimination performance in healthy young adults. Using a single-blind, randomized, sham-controlled, crossover design, six young adults (1 male, 5 females) received both types of brain stimulation (hf-tRNS and sham) in counterbalanced order across two study visits, separated by at least 72 hours. Each visit included three 18-minute stimulation sessions spaced by short breaks. During stimulation, participants performed a demanding motion discrimination task, judging the direction (1 of 8 directions) of moving dot stimuli with varying coherence levels (25-100% in steps of 5%). As expected, motion discrimination accuracy increased linearly with coherence. We fitted psychometric functions using a logit generalized linear model to estimate the coherence threshold at 50% accuracy. Learning slopes were then calculated across the three sessions in each condition. Results showed consistently steeper learning slopes in the hf-tRNS condition compared to sham. These findings suggest that a one-day hf-tRNS over bilateral hMT+ can accelerate perceptual learning in motion discrimination, highlighting its potential for developing time-efficient training interventions to improve visual function in aging and clinical populations.

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**Poster**

## **PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.12/Q6

**Topic:** E.06. Vision

**Support:** NIH T32

**Title:** Homotopic reorganization of the visual word form area following surgical resection of connected cortex

**Authors:** \***B. RISPOLI**<sup>1</sup>, R. CHATTERJEE<sup>2</sup>, K. A. ZAGHLOUL<sup>2</sup>, S. INATI<sup>2</sup>, T. T. LIU<sup>1</sup>;  
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**Abstract:** The visual word form area (VWFA), typically located in the left ventral temporal cortex (VTC), is crucial for word reading due to its privileged connectivity to higher-order visual, semantic, and language areas. One of these higher-order areas, the anterior temporal lobe (ATL), is thought to play an integrative role in language and reading through its involvement in lexical access, semantic processing, and conceptual knowledge. While acute lesions involving the VWFA in adulthood can result in reading impairments (e.g., alexia), the impact of lesions to connected cortex on VWFA function remains unclear. In this study, we ask whether a resection of ATL impacts reading selectivity in the VTC and how outcomes may vary by hemisphere of resection. We analyzed a clinical dataset of patients (n=9) who underwent unilateral resection of ATL during adulthood for the management of drug-resistant epilepsy. Patients completed an fMRI reading task both pre-operatively and one year post-operatively. During the reading task, patients read on-screen stories and viewed a matched control condition. VTC anatomical ROIs were drawn in the native anatomy of each patient's brain for each hemisphere, and mean responses for the reading and control conditions were computed. Reading selectivity was calculated in each ROI as the difference in beta weights between the reading and control conditions for each pre-operative and post-operative session. We found that the hemisphere of resection was predictive of a change in reading selectivity after surgery in the intact, homotopic VTC. Following left ATL resection (n=5), all patients showed a consistent increase in reading selectivity in the intact right VTC. Conversely, patients with right ATL resection (n=4) did not show this pattern, likely because language and reading functions remained lateralized to the left hemisphere. Together, these findings highlight the plasticity of reading-related circuitry in adulthood, showing that disruption of left hemisphere VWFA connectivity via ATL resection may promote compensatory reliance on the intact right VWFA. Importantly, this homotopic reorganization of the VWFA appears to be asymmetric, as no comparable reorganization occurs following right hemisphere ATL resection.

**Disclosures:** **B. Rispoli:** None. **R. Chatterjee:** None. **K.A. Zaghloul:** None. **S. Inati:** None. **T.T. Liu:** None.

**Poster**

## **PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.13/Q7

**Topic:** E.06. Vision

**Support:** National Science and Technology Innovation 2030 Major Program  
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**Title:** Parallel Encoding of Conspecific and Heterospecific Faces in the Human Brain and a Deep Neural Network

**Authors:** \*G. CHEN, X. MA, J. WEI, R. YANG, Y. WANG, Q. WANG, F. FANG;  
Peking Univ., Beijing, China

**Abstract:** Recognizing conspecific faces is a fundamental function of the primate visual system, supported by a well-characterized network of face-selective regions in the ventral stream. However, it remains unclear whether there are neuronal populations in the human neocortex specialized for processing heterospecific (e.g., animal) faces, and whether the processing of human and animal faces recruits overlapping or segregated cortical populations. Although deep convolutional neural networks (DCNNs) can achieve human-level performance in visual recognition, whether their internal representations of human and animal faces align with those in the human brain remains an open question.

To address these issues, we recorded intracranial EEG signals from ten patients with drug-resistant epilepsy implanted with stereo-electrodes while they passively viewed a series of images including human faces, animal faces, and non-face objects. In human higher-order visual areas, including the lateral occipital cortex (LOC) and ventral temporal cortex (VTC), we identified contacts showing a preference for human (human-face-selective contacts) or animal faces (animal-face-selective contacts). Using single-contact spectro-temporal decoding across human-, animal-, and non-face exemplars, we constructed representational dissimilarity matrices (RDMs) for each contact. Neural RDMs were significantly more correlated between contacts within the same category than across different categories, suggesting that human- and animal-face-selective neuronal populations encode conspecific and heterospecific faces with distinct representational geometries.

Similarly, in a pre-trained DCNN (AlexNet), we identified human-face-selective and animal-face-selective units using independent localizers. Within each layer, we obtained model RDMs based on pairwise Euclidean distances in high-dimensional activation space across these units. Notably, only in the deeper layers did model RDMs from human-face-selective units align closely with neural RDMs derived from human-face-selective contacts, suggesting convergence at a similar hierarchical stage. Moreover, lesioning human-face-selective or animal-face-selective units led to dissociable and category-specific recognition impairments, demonstrating their causal roles in conspecific and heterospecific face recognition.

Together, these findings reveal parallel and segregated pathways for conspecific and heterospecific face processing in both human neocortex and DCNNs, highlighting convergent representations of face processing in biological and artificial neural systems.

**Disclosures:** G. Chen: None. X. Ma: None. J. Wei: None. R. Yang: None. Y. Wang: None. Q. Wang: None. F. Fang: None.

## **Poster**

### **PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.14/Q8

**Topic:** E.06. Vision

**Support:** NSERC

**Title:** Influence of TMS-Induced Perturbation of Egocentric and Allocentric Brain Hubs on Reach Accuracy and Precision

**Authors:** \*L. MUSA<sup>1</sup>, G. N. LUABEYA<sup>2</sup>, X. YAN<sup>1</sup>, M. VESIA<sup>4</sup>, J. CRAWFORD<sup>3</sup>;  
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**Abstract: Introduction:** Reaching to spatial targets can rely on egocentric (EGO; relative to the body) or allocentric (ALLO; relative to external landmarks) reference frames. Musa et al. (2025) identified two distinct cortical hubs within the visual peripheral (VP) network (Schaefer et al., 2018) associated with these reference frames: ExstrSup-2 (superior, dorsal stream), linked to both EGO and ALLO, and ExstrInf-2 (inferior, ventral stream), associated specifically with ALLO. This study used transcranial magnetic stimulation (TMS) to test the causal contributions of these hubs to goal-directed reaching. We hypothesized that TMS to ExstrSup-2 would impair EGO-based reaching, while stimulation of either hub would affect ALLO-based reaching due to the transformation of ALLO information into EGO for motor execution (Chen et al., 2018). We also examined whether individual differences in VP network modularity modulate TMS-induced behavioral changes, with the prediction that higher modularity would buffer against disruption. **Methods:** Sixteen participants performed a delayed reach-to-touch task under EGO and ALLO instructions, matched for sensory and motor demands (Musa et al., 2024). Resting-state fMRI was used to identify individual TMS targets and calculate VP network modularity. Triple-pulse TMS (1 Hz, 110% of motor threshold) was applied during the memory delay phase to either ExstrSup-2, ExstrInf-2, or during a control (no-stimulation) condition. Behavioral performance was assessed by accuracy, precision, and reaction time. **Results:** TMS to the superior hub impaired both accuracy and precision across EGO and ALLO tasks. In contrast, stimulation of the inferior hub selectively disrupted accuracy and reduced reaction time in the ALLO task, supporting its specialized function in landmark-based reaching. Higher VP modularity was associated with reduced TMS-induced errors, especially following ExstrSup-2 stimulation.

**Conclusion:** These results provide causal evidence that 1) dorsal stream regions contribute to both egocentric and allocentric reaching, 2) ventral stream regions play a specialized role in allocentric, landmark-based actions, and 3) greater VP network modularity reduces susceptibility to neural perturbation, suggesting a protective role of modular architecture.

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## **Poster**

### **PSTR224: Visual Learning, Memory, and Categorization**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR224.15/Q9

**Topic:** E.06. Vision

**Title:** Perceptual decision-making in juvenile zebrafish

**Authors:** \*A. LAGURIN, F. SVARA, K. L. BRIGGMAN;  
Computat. Neuroethology, Max Planck Inst. for Neurobio. of Behavior, Bonn, Germany

**Abstract:** Animals perceive their environment through the integration of multiple sensory inputs, which can be influenced by experience to guide future decisions. We investigated the plasticity of sensory-guided behavior by manipulating the food preference of juvenile zebrafish, which exhibit more complex conditioning behaviors than larval zebrafish. The juvenile zebrafish brain remains optically accessible and relatively small, which are desirable for whole-brain non-invasive functional imaging and electron microscopy-based connectomics. First, we provided fish with differently colored food particles and quantified any innate preference based on color alone. We then paired the initially preferred food color with a mildly aversive chemical stimulus. After brief training, the fish altered its preference and selectively consumed colored food particles not associated with the aversive stimulus indicating the formation of a multimodal associative memory that persisted beyond the training period. This conditioned preference was absent in trained fish foraging under illumination wavelengths in which food color could not be discriminated. We then used two-photon microscopy to quantify cellular resolution activity using minimally restrained transgenic fish in which the eyes and tail were free to move. Simultaneous recording of neural populations across the juvenile brain in behaving fish enabled us to correlate neural activity with food-related features, including color and palatability. We are currently analyzing the functional data to identify neural populations correlated with the formed associative memory and the observed behavioral plasticity.

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## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**



**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.01/Q10

**Topic:** F.01. Eye Movements

**Support:** NEI R00EY027017-05

**Title:** Characterizing Neural Correlates of internally-generated Eye Movements in Larval Zebrafish

**Authors:** \*S. MUKHERJEE<sup>1</sup>, A. D. RAMIREZ<sup>2</sup>;

<sup>1</sup>Sch. of Grad. Studies, SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; <sup>2</sup>Physiol. and Biophysics, SUNY Downstate, Brooklyn, NY

**Abstract:** The vertebrate visuomotor system enables animals to orient their gaze and movements in response to salient stimuli. One of the key components of this system is the optic tectum (superior colliculus in mammals), a midbrain structure that integrates spatially organized visual input with other sensory modalities to guide orienting and evasive behaviours. While the tectum's stimulus-driven responses are well characterized, it remains relatively unresolved whether the same circuits also contribute to spontaneous or internally-generated eye movements in the absence of visual input. Previous work has shown that spontaneous saccade timing in the larval zebrafish depends on hindbrain neurons exhibiting ramp-to-threshold dynamics. However, a clear role for the tectum and its dynamics in the absence of visual stimulus is yet to be determined. To address this, we investigate horizontal eye movements in larval zebrafish (*Danio rerio*) without visual stimulus. Larval zebrafish are an ideal model due to the conservation of tectal architecture with premotor connections and the accessibility of whole-brain imaging in transparent larvae. Larvae were immobilized in agarose dorsal side up, with space around eyes to facilitate movement and two-photon calcium imaging was used to monitor population-level and single-neuron activity across the brain during spontaneous behaviour. Eye movements were simultaneously recorded with a camera from below the animal. The animal was kept in darkness during the experiment to prevent visual stimulation. Preliminary findings show that no neurons in the tectum are positively correlated with spontaneous horizontal saccades, suggesting that the tectum may not play a role in eye movements in absence of visual stimulus. In addition, we observed activity in the forebrain, pointing to the possibility of an alternative circuit for eye movement control. These findings can potentially expand our understanding of the distributed networks involved in internally-generated motor behaviours.

**Disclosures:** S. Mukherjee: None. A.D. Ramirez: None.

**Poster**

**PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.02/Q11

**Topic:** F.01. Eye Movements

**Support:** NIH Grant R01NS079518  
NIH Grant R01NS129608  
NSF GRFP 241158

**Title:** Premotor mechanisms of saccadic modulation in mouse superior colliculus

**Authors:** \*A. BUTEAU;  
Univ. of Colorado, Anschutz Med. Campus, Aurora, CO

**Abstract:** Animals use ballistic eye movements called saccades to efficiently gather visual information and recenter their gaze as they navigate their environment. During saccadic eye movements, neural activity throughout the visual system is modified such that it becomes difficult to perceive stimuli, a phenomenon referred to as saccadic suppression. A previous study from our lab demonstrated that visual activity in mouse superior colliculus (SC), a highly conserved visuomotor structure, is modulated around the time of saccades (Hunt et al., bioRxiv, 2024). Ex vivo slicework in mice has identified a putative circuit in the SC in which the saccade motor program is used to drive inhibition of visual SC neurons via local inhibitory (GABAergic) neurons; however, this circuit has yet to be examined in-vivo. The goal of this research is to evaluate this proposed mechanism of saccadic modulation by characterizing the role of premotor and inhibitory SC neurons during saccades and determining how both influence visual activity. Using Neuropixels electrodes, we collected extracellular recordings of single-unit activity across visual and motor layers of the SC while mice made saccades. Mice were head-fixed within an immersive visual arena and shown a low-contrast drifting grating stimulus to elicit saccades via the fast phase of the optokinetic reflex. Periodically, the contrast of the grating was briefly elevated to evoke discrete visual responses from visual SC neurons. Using this paradigm, we show that premotor SC neurons represent a motor plan for saccades at the single-unit and population level. We are currently examining simultaneously recorded premotor and visual SC activity, with the goal of addressing how premotor populations may be modulating visual neurons during saccades. In a subset of experiments, we chemogenetically inactivated GABAergic neurons in the intermediate/deep SC. Preliminary results suggest that while these neurons contribute to saccadic modulation, there are additional factors influencing the activity of visual SC neurons. Ongoing opto-tagging experiments aim to more precisely define the role of GABAergic SC neurons and their relationship to both premotor and visual SC neurons during saccades.

**Disclosures:** A. Buteau: None.

**Poster**

**PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #: PSTR225.03/Q12**

**Topic:** F.01. Eye Movements

**Support:** NINDS R01NS079518  
NINDS R01NS129608  
NIH Diversity Supplement 3R01NS079518-12S1

**Title:** Distinct roles of Pitx2+ and Gad2+ neurons in the superior colliculus in saccades

**Authors:** \*C. MINJAREZ<sup>1</sup>, N. FISHER<sup>2</sup>, A. WILLIAMS<sup>3</sup>, A. BUTEAU<sup>4</sup>, J. HUNT<sup>5</sup>, G. FELSEN<sup>6</sup>;

<sup>1</sup>Physiol. and Biophysics, CU Anschutz Med. Campus, Denver, CO; <sup>2</sup>Univ. of Colorado-Denver (UCDenver) (Anschutz Med. Campus), Aurora, CO; <sup>3</sup>Univ. of Colorado Anschutz Med. Campus, Aurora, CO; <sup>4</sup>Physiol. & Biophysics, <sup>5</sup>Univ. of Colorado, Anschutz Med. Campus, Aurora, CO; <sup>6</sup>Dept. of Physiol. and Biophysics, U. of Colorado Sch. of Med., Aurora, CO

**Abstract:** Survival in dynamic environments depends critically on orienting behaviors. Rapid, coordinated actions, like saccades and head turns, reorient sensory organs towards salient stimuli. The intermediate and deep layers of the superior colliculus (SC) are a crucial conductor in orchestrating these complex sensorimotor transformations. However, the cell-type-specific circuitry underlying the selection and initiation of orienting movements is unclear. We hypothesize that functional inhibition mediates competitive interactions between populations of pre-motor neurons, encoding movements to specific targets. We seek to test this hypothesis by examining how the activity of genetically identified Pitx2+ pre-motor SC output neurons and GABAergic SC neurons relates to saccades. In this study, we expressed DREADDs in Pitx2+ and Gad2+ neurons in separate groups of transgenic mice to silence neuronal activity during a protocol that elicits frequent saccades. Comparing saccade parameters -- such as start and endpoints, amplitude, duration, and frequency-- between test and control sessions allows us to determine the necessity of Pitx2+ and Gad2+ neurons in normal saccadic behavior. Preliminary results suggest that inhibiting Pitx2+ neurons has little effect on overall saccade frequency but may affect amplitude. Analyses of our Gad+ inhibition data are ongoing; we expect to observe effects on saccades consistent with long-range inhibition within the SC. Together, these experiments aim to uncover cell-type-specific circuit mechanisms underlying precise orienting movements.

**Disclosures:** C. Minjarez: None. N. Fisher: None. A. Williams: None. A. Buteau: None. J. Hunt: None. G. Felsen: None.

**Poster**

**PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #: PSTR225.04/Q13**

**Topic:** F.01. Eye Movements

**Support:** R01NS079518  
R01NS129608

**Title:** Role of superior colliculus in visually evoked escape response in mice

**Authors:** \*N. FISHER<sup>1</sup>, J. HUNT<sup>2</sup>, G. FELSEN<sup>3</sup>;

<sup>1</sup>Univ. of Colorado-Denver (UCDenver) (Anschutz Med. Campus), Aurora, CO; <sup>2</sup>Univ. of Colorado, Anschutz Med. Campus, Aurora, CO; <sup>3</sup>Dept. of Physiol. and Biophysics, U. of Colorado Sch. of Med., Aurora, CO

**Abstract:** The deep layers of the superior colliculus (dSC) are responsible for initiating orienting behaviors, such as approach and escape behaviors. There are two main descending pathways from these deep layers. One pathway, which can be referred to as the “crossed” pathway, has projections that cross over to the contralateral brainstem to initiate orienting movements, such as saccades, to targets of interest. The other projects ipsilaterally, sometimes referred to as the “uncrossed” pathway, and plays a role in initiating defensive behaviors, such as escape.

However, given the fundamental similarity of orienting movements towards appetitive and away from aversive stimuli, we wondered whether pre-motor neurons responsible for orienting to targets also play a role in orienting away from aversive stimuli. Within the crossed pathway, a subclass of neurons expressing the transcription factor Pitx2+ are involved in the initiation of approach-related orienting motor behaviors. However, it is unclear whether this class of Pitx2+ pre-motor neurons is involved in defensive behaviors.

To address this question, we developed a head-fixed paradigm for studying escape behavior that allows for neural activity underlying escape to be recorded and perturbed in a controlled manner. Head-fixed mice are presented with looming stimuli consisting of a peripherally-presented expanding circle, and attempted escape responses are measured using a force-detecting strain gauge mechanism. Pilot experiments demonstrate the functionality of the system, and we are currently optimizing the stimulus parameters to elicit reproducible escape behavior.

We will next examine the role of Pitx2+ neurons in escape behavior via DREADD-mediated reversible inhibition. If these neurons are also involved in escape behavior, we expect that inhibiting Pitx2+ activity will reduce the frequency and kinematics of the escape response.

Future experiments will use viral tracers to examine the downstream targets of pre-motor SCd neurons that may mediate escape. We are primarily interested in examining the nuclei responsible for communicating from the dSC to the amygdala, which has been implicated in fear-related behaviors, including escape. Regions of interest include the lateral posterior nucleus of the thalamus, the ventral tegmental area, and the dorsal periaqueductal gray matter.

By further exploring the cell types and circuitry responsible for producing orienting behaviors in mice, we aim to further explain the role of the superior colliculus in both approach and escape behaviors, as well as unify our understanding of the circuitry behind these behaviors.

**Disclosures:** N. Fisher: None. J. Hunt: None. G. Felsen: None.

**Poster**

**PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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**Topic:** F.01. Eye Movements

**Support:** Japan Agency for Medical Research and Development (AMED) Brains and Minds Project no. 19dm0207093h0001  
Japan Society for the Promotion of Science (JSPS) Grant-in-Aid for Scientific Research no. 23H03700

**Title:** Expected foveation of target stimuli drives large-scale traveling waves across the visual cortices in primates

**Authors:** \*K. HO<sup>1</sup>, C.-Y. CHEN<sup>2</sup>, H. ONOE<sup>5,2,3</sup>, T. ISA<sup>4,2,3</sup>;

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**Abstract:** Saccades are fast eye movements that drastically change the retinal visual inputs. Previous studies showed that after saccades, traveling waves (TWs) of local field potential occur in the cortical visual areas. Our recent electrocorticogram data from 2 marmosets performing visually-guided saccades (VGS) revealed post-saccadic, large-scale TWs during 0~75 ms after saccade offset, originating from caudal V1 and propagate ventro-rostrally (peripheral to foveal representation in V1) across the whole occipital cortices, which may be accountable for previous observations. Yet, it remains unclear if these TWs are caused by the saccadic efference copy, the accompanying retinal shift of visual stimuli, or both. To answer this question, we looked at the brain activity around spontaneous saccades while the screen displayed no stimulus (NS), or artificial saccades (AS, shifting a peripheral stimulus to the center of gaze during fixation at saccadic speed). The former contains only the motor and the latter only the sensory component of saccades. In the NS condition, the TWs start right after saccade onset (~30 ms before offset), spreading from area MT/V5. In the AS condition, the TWs start at 30 ms after stimuli reach the center of gaze, originating from ventral occipital cortices and spread dorso-anteriorly. In addition, the VGS waves are highly consistent across trials especially for saccades contraversive to the electrodes, but the AS and NS waves are less consistent and show little directional difference. Neither the AS waves, the NS waves, nor their sum resembles the TWs after VGS. To further investigate the interaction between the sensory and motor components of saccades, we analyzed the post-saccadic TWs while a gaze-contingent (GC) stimulus was displayed on the screen. This design keeps the stimulus while minimizing its retinal shift caused by saccades. Based on the difference between stimulus and saccade direction, we separate the GC saccades into pro-saccades (GC<sub>pro</sub>, < 22.5°) and anti-saccades (GC<sub>anti</sub>, > 90°). In the GC<sub>pro</sub> condition, TWs are similar to VGS in terms of onset timing, spatiotemporal pattern, and directional difference. In contrast, TWs in the GC<sub>anti</sub> condition show no such similarities. Notably, in the GC<sub>pro</sub> condition, at ~75 ms after saccade offset (when a typical VGS wave ends), a subsequent wave starts from rostral occipital areas and goes caudally. In conclusion, our results suggest that the TWs after VGS may reflect the expected foveation of the target stimulus, rather than the saccadic efference copy or the retinal shift alone. The subsequent wave in the GC<sub>pro</sub> condition may signal the prediction error if the target does not reach the fovea as expected.

**Disclosures:** K. Ho: None. C. Chen: None. H. Onoe: None. T. Isa: None.

**Poster**

**PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.06/Q15

**Topic:** F.01. Eye Movements

**Support:** RS-2023-NR077084  
RS-2023-00217361  
RS-2025-00518788  
RS-2025-02263832

**Title:** Inhibitory adjustment of firing threshold in visual cortical area explains how motion prediction enhances sensorimotor behavior

**Authors:** \*J. AHN<sup>1,2</sup>, S. KIM<sup>1,3</sup>, S. WOO<sup>1,3</sup>, J. LEE<sup>1,2,3</sup>;

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**Abstract:** Organisms actively utilize prior knowledge to adapt to changing environments, especially when sensory input is ambiguous. Previous studies have shown that expectations about motion direction sharpen the population tuning of middle temporal (MT) neurons, enhancing smooth pursuit eye movements, and this behavioral improvement is particularly evident under sensory uncertainty. However, the underlying neural mechanism remains unclear. Here, we used a recurrent neural network (RNN) model to examine how prior expectations improve behavior by sharpening visual neuron population tuning. Model neurons with preferred directions deviating from the expected direction showed elevated response thresholds, indicating selective suppression. This sharpened tuning around the expected direction and reduced trial-by-trial variability in eye movements, resulted in more consistent behavior. These effects were prominent under low-contrast (ambiguous) stimuli but negligible under high-contrast conditions. Furthermore, noise-driven spontaneous neural activity exhibited biased population responses toward the expected direction. This was accompanied by behavioral directional biases, in eye movements. To validate the model's prediction of selective inhibition, we recorded local field potentials (LFPs) in macaque MT neurons using a laminar probe as a proxy for membrane potential. We found that delta-frequency power significantly decreased as the difference between a neuron's preferred and expected direction increased. This supports the model's prediction and indicates inhibitory modulation of neuronal thresholds in MT. Together, our findings suggest that expectation enhances behavior via inhibitory threshold modulation in visual cortical neurons. This work provides a mechanistic account of how expectation sharpens neural tuning and stabilizes behavior, highlighting feedback inhibition in the sensory cortex as a key component of expectation-driven neural computation.

**Disclosures:** J. Ahn: None. S. Kim: None. S. Woo: None. J. Lee: None.

**Poster**

**PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.07/Q16

**Topic:** F.01. Eye Movements

**Support:** NIH Grant EY036728  
NIH Grant EY025172

**Title:** Investigating the neural substrates of history dependent associations: How under urgent conditions recent experience conflicts or colludes with ongoing cognitive goals to direct behavior

**Authors:** \*E. KATTNER<sup>1</sup>, E. SALINAS<sup>2</sup>, T. R. STANFORD<sup>3</sup>;

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**Abstract:** Visual attention enables organisms to select locations in space that may contain behaviorally relevant stimuli and relies on the interplay between sensory-driven exogenous, experience-dependent, history-based, and cognitively driven endogenous mechanisms. However, given the potential for conflict between recent experience and current goals, this interaction is complex. Consequently, it remains to be seen how these mechanisms are governed by activity in oculomotor areas such as the frontal eye field (FEF). To examine this, we developed and trained two monkey subjects on an urgent rock-paper-scissors (RPS) paradigm where subjects make judgments between two differently colored stimuli, with each trial presenting 2 of 3 possible colors (red, yellow, blue). Choices are reported with a saccade to the higher value stimulus (target) according to the rule ( $R > Y$ ,  $Y > B$ ,  $B > R$ ), and by controlling the probability of a rule switch or repeat, we can investigate interactions between recent history and current task demands. Giving the signal to make a choice before the onset of the cue colors makes the task urgent, allowing for the computation of processing time (PT), or how long the cue information is present before the choice. Plotting performance as a function of PT yields tachometric curves, psychometric functions that track performance with millisecond resolution. Here, performance depends on PT, taking ~200ms to reach asymptote, and saturating at ~72% correct, reflecting the difficulty of task switching. Naturally, trials involve the repetition of a rule, an “easy” switch where what was the distracter becomes the target ( $R$  v.  $Y \rightarrow Y$  v.  $B$ ), or a “hard” switch where what was the target becomes the distracter ( $R$  v.  $Y \rightarrow B$  v.  $R$ ). Repetitions enhance performance while easy switches take longer to reach lower overall asymptotes. Hard switches result in worse performance still, falling below 50% across a range of PT (120-250ms), reaching asymptote at ~325 ms. Thus, at intermediate PTs behavior is guided, primarily, by prior experience, with more PT required to accurately execute task rules which, critically, the subjects do easily under non-urgent conditions. Accompanying these findings are preliminary electrophysiological results

from FEF neurons (n=49) recorded from the same monkey subjects. The data reveal slight, yet potentially significant, differences in presaccadic activity for both correct and incorrect responses in each of the trial conditions (repeats, easy switches, hard switches). In all, this suggests that history-dependent mechanisms dominate behavior at early timescales, preceding the retrieval of cognitive goals, and oculomotor activity reflects this.

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## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.08/R1

**Topic:** F.01. Eye Movements

**Support:** ANR-18-CE37-0008

**Title:** Investigating waiting impulsivity using a four-choice serial reaction time task in macaque monkeys

**Authors:** \*J. LOAYZA<sup>1</sup>, M. BASHAIWETH<sup>2</sup>, T. ORSET<sup>1</sup>, T.-M. SARTORIS<sup>1</sup>, Y. WORBE<sup>1</sup>, J.-F. AUBRY<sup>2</sup>, P. POUGET<sup>1</sup>;

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**Abstract:** Impulsivity is a tendency to act quickly, without adequate consideration of consequences. Waiting impulsivity, also known as premature or anticipatory responses, is the inability to restrain an action before an appropriate moment. Here, we aimed to investigate the timing of premature or anticipatory responses in monkeys.

Data was collected from two 5-year old male *Macaca fascicularis* monkeys. Monkeys were trained in a four-choice serial reaction time eye-movement task whilst sitting, head fixated, in a primate chair and looking at a screen. The task required central fixation for 200 ms, followed by a correct eye movement to a square in which a green dot (the target) appeared. The dot appeared randomly in one of four possible squares for 150 ms. Following a successful trial, a bolus of juice was delivered to the monkeys' mouth. Eye movements were recorded using EyeLink (1k, Version 4.56, SR-Research Ltd, Mississauga, Ontario, Canada), which was connected to an analog-to-digital converter (Plexon Inc, TX, USA). The task was run on EventIDE software (OkazoLab Ltd, Netherlands). Data was collected using Plexon software and analysed using MATLAB. Saccadic latency was calculated as the time interval between target onset and the initiation of the first eye movement following central fixation, with negative values reflecting anticipatory or premature saccadic responses.

Data from nine sessions with monkey D and two sessions with monkey H were analyzed. A total of 1858 trials from monkey D and 85 trials from monkey H were included in the analysis. For



Monkey D, an average of 9.26% (SD = 2.54%) of saccades were initiated before the target was presented, while for Monkey H, the average was also 9.26%, but with a higher variability (SD = 9.72%).

In an oculomotor version of a four-choice serial reaction time task, we observed significant variability in saccadic latency among both monkeys, indicating inconsistent response timing across trials. Notably, for both monkeys, on average 9.26% of saccades were initiated before the target was presented, suggesting impulsive behavior. The ability to appropriately time a response is a crucial cognitive skill that is affected by various disorders, including addiction and attention deficit hyperactivity disorder (ADHD). Our ongoing research (currently in preparation) investigates the use of transcranial focused ultrasound stimulation to explore whether different types of impulsive behavior can be modified by targeting distinct areas within the oculomotor system.

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## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.09/R2

**Topic:** F.01. Eye Movements

**Title:** Peripheral proxy of the central nervous system: Investigation of the Wilson's phenomenon

**Authors:** \*T. POITOU<sup>1</sup>, P. DAYE<sup>2</sup>, P. POUGET<sup>3</sup>;

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**Abstract:** Combined movements of the eyes and ears, as well as the head, are common in animals. In 1908, Wilson first described an association between eye and ear movement in humans. This phenomenon was later described by Heuser (1976), which he named the oculo-auricular phenomenon. Later, in 1993, Urban and al. showed that this activation of ear movement, attributed to the transverse auricular muscle (TAM), is not exclusive to eye movements and can also be triggered by head movements, combined or not with eye movements. In humans, a vestigial connection, always present at the electromyographic level, allows for the investigation of vestigial anatomical connections responsible for these co-activations. Various studies on animal models show connections passing through the superior colliculus, the paramedian pontine reticular formation, and the facial nerve nucleus responsible for the TAM innervation. The connections proposed so far only partially explain this co-activation, in particular during eccentric gaze fixation. Our study aims to question the current knowledge of the existing circuitry involved in the oculo-auricular phenomenon. First, we reproduced the experimental conditions and results that were already obtained and added a quantitative analysis of the electromyographic and eye-tracking signals. Then, we added a series of new tests to

question some properties of the link between the TAM co-activation and the oculomotor behavior in the light of the known anatomical circuitry. Our first exploratory results show that this co-activation is characterized above all by contralateral activation. Activation is more marked in amplitude and also appears to be earlier. This co-activation is found in saccade, pursuit and fixation paradigms, during eccentric gaze. There is also activation during active and passive head movements, with and without gaze deviation. We find a co-activation during a saccade request with eyes closed, with a different profile. Altogether these results could serve as a peripheral proxy for central activation; both in experimental studies and for clinical/diagnostic purposes.

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**Disclosures:** **T. Poitou:** A. Employment/Salary (full or part-time): P3Lab (neuroclues). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); P3Lab (neuroclues). **P. Daye:** A. Employment/Salary (full or part-time): P3Lab (neuroclues). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); P3Lab (neuroclues). **P. Pouget:** A. Employment/Salary (full or part-time): P3Lab (neuroclues). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); P3Lab (neuroclues).

## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.10/R3

**Topic:** F.01. Eye Movements

**Title:** Video-eyetracker calibration principles revisited in the eyes of oculomotor biomarkers computation.

**Authors:** \*P. M. DAYE<sup>1</sup>, P. POUGET<sup>2</sup>;

<sup>1</sup>P3Lab, UMon, Louvain-la-Neuve, Belgium; <sup>2</sup>Paris Brain Inst., Paris, France

**Abstract:** Video-eyetrackers are currently used in a large set of applications, from the study of eye movements in research settings to the support of neurological disorders diagnosis. Traditionally, an oculomotor setup is composed of a protocol presentation device and a video-eyetracker that records the motion of the eye. To allow the experimenter to evaluate where a subject is looking during an evaluation task, the subject must undergo a calibration procedure that allows the computation of a transformation mapping between the video-eyetracker reference frame and the presentation device reference frame. Several studies have analyzed the quality of

the calibration process, but to the best of our knowledge, no studies have looked at the sensitivity of the oculomotor biomarkers to a default of the calibration mapping. To achieve that goal, we built a Python simulator of a generic oculomotor research setup. We used this simulator to assess the effects of a deviation from an ideal calibration between the calibration process and the following oculomotor tasks. Our simulations demonstrate that first-order calibration mappings are less accurate but more robust than higher-order calibration mappings. If the biomarkers' sensitivity to an imperfect calibration is more important for higher-order mappings, we show that it can be reduced through a careful correction of the recorded signal during the calibration. Our simulations also allow us to predict the statistically relevant range of values that can be extracted from the recorded data, challenging the accuracy/precision usually reported in studies.

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## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.11/R4

**Topic:** F.01. Eye Movements

**Support:** ANR-21-CE37-0018-01

**Title:** Eye movements reflect perceptual alternations in multistable motion stimuli

**Authors:** \***V. MYRODIA**<sup>1,2</sup>, A. MONTAGNINI<sup>2</sup>, L. MADELAIN<sup>1</sup>;

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**Abstract:** During the viewing of ambiguous multistable stimuli, perception spontaneously alternates between competing interpretations despite constant sensory input. To study the link between perceptual switching and tracking eye movements we designed a paradigm that jointly measures smooth pursuit and perceptual reports during multistable motion. The stimulus was a spatially extended, bistable version of the classic motion quartet (ExtMQ). We tested the hypothesis that smooth pursuit provides a continuous, real-time proxy for perceived motion direction, which we inferred from explicit perceptual judgments. Human subjects (N=22) viewed an ExtMQ stimulus comprising two alternating dot grids. Each grid corresponded to one image in a pair, and their alternation induced apparent motion. The grids spanned a large portion of the visual field, allowing for sustained smooth pursuit. By varying the horizontal and vertical spacing between dots (aspect ratio), we were able to bias perception toward horizontal or vertical motion while maintaining stimulus ambiguity. Participants were instructed to follow the perceived motion and to report its direction upon an auditory beep (occurring randomly, with and average inter-beep interval ~4 seconds). Each trial lasted 20 s. Eye movements were recorded using an EyeLink 1000 eye-tracker. The experiment included two sessions. In Session 1, we

sampled a large range of aspect ratios to estimate individual perceptual biases. In Session 2, we presented stimuli with personalized ambiguity levels (corresponding to 25%, 50%, 75% preference for vertical motion perception). Using a 1D-CNN network [Startsev et al. 2018], we classified epochs of smooth pursuit eye movements and compared them to perceptual reports. We found a strong and statistically significant correlation between pursuit direction and perceptual reports across participants and conditions ( $r = 0.74$ ,  $p < 0.001$ ). Overall, pursuit showed a horizontal bias, mirroring the dominance of horizontal percepts. Switches were most frequent at intermediate ambiguity (50%), with four times more alternations than at 25%. The 75% threshold was also perceived as more ambiguous than the 25% threshold, resulting in twice as many switches. Saccade direction proved to be a reliable predictor of perceptual switches, supporting their diagnostic value for tracking perceptual state changes. These findings confirm a robust statistical relationship between pursuit and perceived motion in multistable displays, while also underscoring the distinct role of saccades. Our paradigm offers a promising tool to examine the temporal dynamics of perception-action coupling in visual disambiguation.

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## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.12/R5

**Topic:** F.01. Eye Movements

**Support:** ZICMH002884

**Title:** Auditory-cued voluntary saccades show robust layer activation in frontal eye field and midbrain oculomotor networks at 7 Tesla fMRI

**Authors:** \*B. AKIN<sup>1</sup>, S. I. KRONEMER<sup>2</sup>, T. MORGAN<sup>3</sup>, D. A. HANDWERKER<sup>4</sup>, R. HUBER<sup>5</sup>, P. BANDETTINI<sup>2</sup>;

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## **Abstract: Introduction**

Voluntary saccades engage cortical and subcortical regions involved in motor planning, attention, and executive control. We used ultra-high field 7T fMRI with parallel transmission (pTx) and high-acceleration GRAPPA (R=16), termed FRISGO, to examine layer-specific activation during auditory-cued saccades, targeting FEF, SEF, caudate nucleus, and DLPFC. The DLPFC supports preparatory control, while FEF/SEF and caudate mediate execution. Preliminary laminar and temporal findings suggest a bidirectional saccade pathway: top-down from prefrontal cortex to caudate, and bottom-up from caudate to FEF/SEF, consistent with cortico-striatal-thalamo-cortical circuitry (Leigh et al 2004).

## Materials & Methods

Healthy adults (2F, 2M, age 27) performed sparse event-related saccade tasks, they are instructed to keep their eyes closed throughout the task and respond to auditory cues presented unilaterally to either the left or right ear. A high-pitch "tick" tone signaled them to initiate a saccade toward the side of the stimulus, while a low-pitch "tock" tone required no response. This design allowed isolation of volitional saccade-related activity from auditory processing by including both go (tick) and no-go (tock) trials.

Data were acquired using a Siemens Nova 8Tx/32Rx coil at 0.85 mm isotropic resolution (TE=19.5 ms; FA=25; TR1=58.5 ms; TR2=4817 ms; TI1=1356 ms, FOV) across three 11-min runs.

## Results&Conclusion

Robust tSNR, both in midbrain and frontal cortical areas, demonstrating pTx efficacy in subcortical imaging (Huber et al 2025). Subject- and group-level GLMs, showed consistent activation in bilateral FEF, SEF, DLPFC, and caudate. Time-course analysis revealed early sustained FEF activity . DLPFC and caudate tracked trial structure, reflecting contextual control. No directional lateralization was observed. Layer analysis indicated mid-layer FEF/SEF activity and feedback in DLPFC . These results support a distributed saccade network and underscore 7T pTx-fMRI's utility in capturing oculomotor dynamics in layer specific resolution. Future work should incorporate attention-driven paradigms and connectivity-based modeling to further dissect the interaction of saccade-related circuits with large-scale brain networks.

## References

Leigh, R.J., & Kennard, C. (2004). *Using saccades as a research tool in the clinical neurosciences*. Brain, 127(3), 460-477. <https://doi.org/10.1093/brain/awh035>

Huber, R., et al. (2025). *Advanced Echo-planar Parallel Imaging with Gradient Harmonization (FRISGO): An optimization strategy for fast high-resolution fMRI*. ISMRM, 2025.

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## Poster

**PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.13/R6

**Topic:** F.01. Eye Movements

**Title:** Eye Movement Strategies and Shot Direction Prediction in Handball Goalkeepers: A Comparison Between Experts and Novices

**Authors:** T. HIRATA<sup>1</sup>, \*M. KAWASUMI<sup>3,2</sup>;

<sup>1</sup>Information Sci., <sup>2</sup>Meijo Univ. Grad. Sch. of Sci. and Engin., Nagoya, Japan; <sup>3</sup>名城大学, 愛知, Japan

**Abstract:** This study aims to explore and clarify eye movement characteristics that affect prediction accuracy. In ball sports with goalkeepers (GKs) such as soccer and handball, their saving ability plays a crucial role in determining match outcomes, especially during penalty kick (PK) in soccer and penalty throw (PT) in handball. In the scene of PT in handball, a shooter is only seven meters away from a goal, therefore a GK must predict the shooting direction quickly and begin his movement before the ball is released from the shooter. The GKs' predictions rely on visual information, and differences in prediction accuracy among individuals subjects. Understanding how GKs visually track the shooter is therefore essential, with eye movement patterns offering a potential indicator. Previous research (Loffting et al., 2015) compared the eye movements of professional and novice GKs, revealing differences in the number of saccades. However, it only focused on the number of saccades and did not examine other aspects of eye movements characteristics. In the present study, five professional and five novice GKs answered the predicted shooting direction after watching PT videos from a GK's perspective, and binocular eye movements were measured by an eye-tracking system during the task. Results showed that the course prediction accuracy of professional GKs was generally higher than that of novices. Furthermore, participants with greater prediction accuracy were found to fixate their gaze on areas other than the ball, indicating differences in attentional focus. These findings suggest that training visual strategies—particularly eye movement patterns—may enhance shooting prediction abilities and also contribute to the analysis of the skills of professional GKs.

**Disclosures:** T. Hirata: None. M. Kawasumi: None.

## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.14/R7

**Topic:** F.01. Eye Movements

**Support:** UTSA HCAP Research Seed Grant

**Title:** Development of predictive oculomotor control in children in relation to a projectile's location and timing

**Authors:** \*M. VASKO, S.-W. PARK;  
Kinesiology, The Univ. of Texas at San Antonio, San Antonio, TX

**Abstract:** Successful completion of everyday tasks relies upon our ability to perceive, predict, and respond to motion within our environment. Past research on the development of oculomotor control has largely focused on the gain in smooth pursuit in infancy. However, developmental changes of gaze stability and strategies in childhood remain elusive in the context of predictive motor behavior. To investigate age-related changes in predictive oculomotor control, typically developing children aged 7 to 12 ( $n = 19$ , age =  $9.4 \pm 1.5$ , 8 females and 11 males) performed two different sensorimotor tasks that involved a projectile, in which the second half of the

trajectory was occluded. The first task required children to predict the final location, and the second task required children to estimate the timing of a projectile at a specific location. Both tasks required the children to anticipate the consequence of the projectile based on the first half of the trajectory. Eye gaze was collected using a remote eye tracking system (Eyelink 1000plus, SR Research). The onset latency of corrective saccades to begin smooth pursuit of the projectile serves as a measure of response preparation, motion sampling, and predictive encoding. In the short time period before the saccade begins, the individual must sample the velocity and trajectory, form a predictive model, and then prepare to move their eyes to the anticipated location. Gaze variability and ball tracking serve as measures of anticipatory oculomotor control, as more accurate internal representations will lead to more consistent oculomotor control and more precise tracking of the ball with the center of the gaze. Accordingly, our hypothesis is that in older children, there will be a decrease in latency for corrective saccades, more accurate smooth pursuit of the projectile, and reduced variability of eye gaze across trials. In the first task, results showed significant Spearman's correlation coefficients ( $p < 0.05$ ) between age and reduced latency to the onset of saccades ( $r = 0.54$ ), reduced gaze variability ( $r = 0.59$ ), and increased tracking of the ball's trajectory ( $r = 0.60$ ). In the second task, results showed a strong correlation between age and the performance outcome, i.e., the accuracy of the time estimation ( $r = 0.75$ ,  $p < 0.001$ ). In contrast, no age-related change in the eye gaze kinematics was found. Altogether, these results suggest the continued development of predictive oculomotor control during a prolonged period of neurophysiological development in childhood. Future studies will identify developmental changes in adolescence.

**Disclosures:** M. Vasko: None. S. Park: None.

## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.15/R8

**Topic:** F.01. Eye Movements

**Support:** NIH Grant 1R01EY034626

**Title:** Midline pursuit dynamics are different in each eye during binocular and monocular viewing

**Authors:** \*S. N. WATAMANIUK<sup>1,2</sup>, D. SINGH<sup>2</sup>, A. CHANDNA<sup>2</sup>, S. J. HEINEN<sup>2</sup>;  
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**Abstract:** Previously we reported that during smooth pursuit of a target moving on the midline, a covered eye rotated out of phase with the target (Chandna et al., 2021). However, because the stimulus moved with a continuous sinusoidal profile, it could not be determined whether the covered eye lagged behind or led the target. Here we evaluate the temporal initiation (latency)

and other dynamics of midline pursuit in binocular and monocular conditions in discrete trials in which the target moved towards or away from the observer. Observers pursued a physical accommodative target (circular array of letters) that moved in depth on a track aligned with the optical midline (peak vel. = 30 cm/s). The stimulus started 50 cm from the observer and after a random fixation time moved towards (50-33 cm) or away (50-67 cm) from them, chosen at random. After a second random fixation period (1-2 sec), observers pursued the target as it moved in the opposite direction back to its initial starting position. Viewing was binocular, or monocular with one eye obscured with an infrared pass filter. An EyeLink 1000+ measured both eyes' movements. Under monocular viewing, the occluded eye often had a longer latency than the viewing eye, but sometimes anticipated the target with a shorter latency, while in other trials it remained stationary. Curiously, even during binocular viewing pursuit initiation in the two eyes was asynchronous, with latencies often differing by 100 msec or more. Eye velocities also differed between eyes, but the difference was greater under monocular viewing. The data refute the idea that a single motor command drives the eyes (Hering, 1868), at least during midline pursuit. Instead, each eye appears to be controlled independently. Our results are consistent with a new hybrid model of binocular control with independent eye command components.

**Disclosures:** S.N. Watamaniuk: None. D. Singh: None. A. Chandna: None. S.J. Heinen: None.

## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.16/R9

**Topic:** F.01. Eye Movements

**Support:** Neurosciences Division of the Canadian Physiotherapy Association (NC)  
Canada Research Chairs program (KEM)

**Title:** Gaze behaviour during walking tasks in ambulatory individuals with spinal cord injury/disease

**Authors:** \*N. CESCA<sup>1,3</sup>, K. CHAN<sup>3</sup>, K. E. MUSSELMAN<sup>1,3,2</sup>;

<sup>1</sup>Rehabil. Sci. Institute, Temerty Fac. of Med., <sup>2</sup>Dept. of Physical Therapy, Temerty Fac. of Med., Univ. of Toronto, Toronto, ON, Canada; <sup>3</sup>KITE- Toronto Rehabil. Inst., Univ. Hlth. Network, Toronto, ON, Canada

**Abstract: Background:** Individuals with incomplete spinal cord injury/disease (SCI) often have difficulty with complex walking tasks (e.g., obstacle negotiation) due to impaired gait adaptability (i.e., ability to adjust walking pattern to task demands). This limitation increases the risk of falls and limits community walking. Visual input is critical for modulating walking patterns; yet, how individuals with SCI use vision (i.e., gaze behaviour) during walking remains poorly understood. **Objective:** To compare gaze behaviour during gait adaptability tasks



between individuals with SCI and age- and sex-matched individuals without SCI. **Methods:** This cross-sectional study involved three walking tasks: 1) walking around an obstacle (i.e., 32-gallon cylindrical trash can), 2) stepping over an obstacle (i.e., 3-inch-high Styrofoam block), and 3) stepping onto a wooden platform (i.e., step height 7.75 inches). Gaze behaviour was recorded at 200 Hz using Pupil Invisible glasses© and analyzed in Pupil Cloud© to identify fixations (i.e., steady gaze) and define common areas of interest (AOIs) (i.e., regions of directed gaze). Gaze metrics (i.e., proportion of participants with at least one fixation on an AOI, number of fixations, average fixation duration) were calculated for the two steps preceding each task. Footfall timing was recorded using the Zeno™ Walkway system to align gaze with step events. Walking speed was measured with a stopwatch. Mann-Whitney U and Fisher's exact tests were used for group comparisons; Cohen's d was calculated to estimate effect sizes for fixation durations. **Results:** Eight individuals with SCI ( $57.6 \pm 15.1$  years; 3 females) and seven without SCI ( $54.1 \pm 15.0$  years; 3 females) participated. All individuals with SCI were independent walkers with non-traumatic injuries (C1-L5). Walking speeds were significantly slower in the SCI group for all tasks ( $p < 0.04$ ). Task 1: More SCI participants fixated on the next footfall beside the obstacle (100% vs. 42.9%;  $p = 0.026$ ). Other gaze metrics were not significantly different; however, fixation duration showed a large effect size ( $d = 1.0$ ). Tasks 2 and 3: No significant group differences in gaze metrics; however, fixation duration showed a moderate effect size ( $d = 0.5$ ) on the obstacle in Task 2, and a large effect size ( $d = 0.9$ ) on the far environment in Task 3. **Conclusions:** Despite slower walking speeds after SCI, gaze behaviour during walking tasks did not significantly differ between groups. However, moderate to large effect sizes suggest differences worth investigating. A larger sample is needed for statistical power and to explore the potential of gaze metrics as targets for walking training after SCI.

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## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.17/R10

**Topic:** F.01. Eye Movements

**Support:** NIH Grant R01EY034626  
Smith-Kettlewell Eye Research Institute  
Wright State University

**Title:** Turning a blind eye: eye movement control without vision

**Authors:** \*S. J. HEINEN<sup>1</sup>, D. SINGH<sup>1</sup>, A. CHANDNA<sup>1</sup>, S. N. WATAMANIUK<sup>2</sup>;

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**Abstract:** We previously showed that an occluded eye moves unpredictably during vergence pursuit, suggesting the eyes are controlled independently (Chandna et al., 2021). However, during tangent screen pursuit occluded and viewing eyes move similarly, suggesting they are controlled as a pair. It could be that the eyes are completely controlled independently (Helmholtz, 1867), or that they are controlled together (Hering, 1868) but only for conjugate movements. If the eyes are only driven independently, an eye without visual input should fail to move. Here we investigate this by recording eye movements from a patient blinded in one eye, yielding no visual input to its independent controller, as opposed to non-zero inputs when an eye is occluded. The patient, a 57 YO female, lost sight in one eye following retinal ischemia at the age of 49 but had corrected to normal acuity in the fellow eye. The vergence target was an accommodative stimulus: a single central letter surrounded by an array of 7 peripheral letters moving back and forth periodically on the midline. The conjugate target was a small dot moving left and right periodically on a tangent screen. Eye movements were measured with an EyeLink eyetracker. We found that the fellow eye followed the target accurately in both paradigms. However, while the blind eye exhibited vergence during midline pursuit, its amplitude and temporal relationship with the target and fellow eye were highly variable. In contrast, the blind eye moved with the target accurately on the tangent screen, with a temporal relationship tightly linked to the target and fellow eye. Catch-up saccades during both paradigms were always binocular. The results provide additional evidence that a single command does not drive both eyes during vergence, but a single command does appear to drive the eyes together during conjugate eye movements, evidence of a hybrid oculomotor system combining Helmholtz's and Hering's theories. The independent controllers may function in the absence of vision via an imperfect internal representation of the target (a "virtual target"). The results have implications for understanding oculomotor neural pathways, and clinical interventions in strabismus.

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## **Poster**

### **PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.18/R11

**Topic:** F.01. Eye Movements

**Support:** NIH MINDS Grant R15NS121788

**Title:** Oculomotor biomarkers of concussion: insights from a multi-component eye-tracking study

**Authors:** D. LIERNUR<sup>1</sup>, M. NEEKI<sup>2</sup>, N. MARSH<sup>1</sup>, C. NEEKI<sup>3</sup>, E. GILL<sup>4</sup>, V. BHATT<sup>1</sup>, S. MARTINEZ-CONDE<sup>5</sup>, S. L. MACKNIK<sup>6</sup>, \*N. M. BRUNET<sup>1</sup>;

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Riverside, CA; <sup>5</sup>Dept. of Ophthalmology, State Univ. of New York Downstate Med. Ctr., Brooklyn, NY; <sup>6</sup>Dept. of Ophthalmology., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY

### **Abstract: 1. Introduction:**

Diagnosing mild traumatic brain injury (mTBI) remains a significant clinical challenge due to the subtlety and variability of symptoms. Traditional assessments often lack sensitivity to detect lingering neurophysiological impairments. Given that approximately 30-50% of the cerebral cortex is dedicated to processing visual information, eye movement behavior offers a promising, non-invasive biomarker for concussion. We developed a novel oculomotor paradigm designed to probe a wide range of brain regions and eye movement systems, to determine whether outdoor patients who sought care following a head injury exhibit distinct oculomotor signatures compared to healthy controls.

### **2. Methods:**

Participants included 170 healthy adults and 30 patients seen as outpatients for head injury at Arrowhead Regional Medical Center. All participants completed an identical 25-minute eye-tracking task consisting of eight subtasks (e.g., smooth pursuit, fixation, memory-guided and reflexive saccades, anti-saccades, free viewing). Eye movements were recorded using the EyeLink 1000 Plus at 500 Hz. For each task, multiple oculomotor metrics were extracted, including saccade amplitude, latency, velocity, and microsaccade dynamics. Data were analyzed using a multivariate Deviation Index (DI) and a random forest classifier to assess group-level and individual-level discrimination.

### **3. Results:**

Results revealed significant differences in oculomotor behavior between mTBI patients and controls across multiple task domains. The Deviation Index was significantly higher in the patient group ( $p \sim 0$ ), reflecting widespread and subtle disruptions in oculomotor control. Additionally, a random forest classifier achieved 93.1% accuracy in distinguishing concussed individuals from healthy participants, even with minimal preprocessing and modest sample sizes. These findings suggest robust and generalizable oculomotor deviations following mTBI.

### **4. Conclusion:**

Our findings provide strong evidence that oculomotor behavior, as measured through a multi-component task, reliably differentiates mTBI patients from healthy controls. The high classification accuracy and wide range of disrupted metrics support the potential use of eye-tracking as an objective biomarker for concussion detection. Future longitudinal research is underway to evaluate whether these deviations persist or resolve over time.

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### **Poster**

**PSTR225: Eye Movements: Central Mechanisms, Perception, Cognition, and Saccades**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR225.19/R12

**Topic:** F.01. Eye Movements

**Title:** Gravity-dependent modulation of downbeat nystagmus: insights from velocity-storage dysfunction

**Authors:** J.-H. PARK<sup>1</sup>, \*J.-Y. CHOI<sup>2</sup>;

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**Abstract:** Downbeat nystagmus, a hallmark of cerebellar dysfunction, varies in intensity depending on head position with respect to gravity—a phenomenon termed gravity-dependent positional modulation. A typical feature of this modulation is its enhancement in the prone (face-down) position and attenuation in the supine (face-up) position, yet its pathophysiological mechanism remains unclear. We recorded eye movements of 10 patients with cerebellar downbeat nystagmus at different head positions along the pitch (interaural) and roll (naso-occipital) axes. Sine-wave fitting decomposed nystagmus into a gravity-dependent component (amplitude and phase shift) and a gravity-independent offset, relative to head-centered gravity orientation. The pitch-axis modulation of the gravity-dependent component was homogeneous across patients, with a median amplitude of 4.1°/s (interquartile range (IQR), 3.2) and a phase shift of 162.9° (IQR 56.7). The roll-axis modulation showed an amplitude of 2.1°/s (IQR 1.6) and a phase shift of 189.5° (IQR 198.8), which could be clustered into two subgroups with the phase shifts near 90° and 270°. The amplitude of gravity-dependent component was significantly larger during pitch-axis modulation than during roll-axis modulation ( $p < 0.05$ ). To determine the underlying mechanisms, we applied a velocity-storage model simulating brain function involved in estimation of rotational velocity, gravity orientation, and inertial acceleration. Into this model, we incorporated a cerebellar lesion that affects the gravity estimator and introduced a head-centered gravity bias. This generated a persistent rotational cue that modulates the nystagmus intensity in a pattern similar to that observed in our patients. The model could additionally explain the variation in phase shifts as well as the weaker modulation of downbeat nystagmus around the roll-axis. These results provide a computational framework for the gravity-dependent modulation of downbeat nystagmus due to cerebellar lesions.

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## **Poster**

### **PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.01/R13

**Topic:** F.04. Voluntary Movements

**Title:** Frontal theta rhythms reflect individual differences in flexible motor plan switching

**Authors:** \*M. ITO<sup>1</sup>, S. IWAMA<sup>2</sup>, J. USHIBA<sup>3</sup>;

<sup>2</sup>Grad. Sch. of Sci. and Technol., <sup>1</sup>Keio Univ., Yokohama, Japan; <sup>3</sup>Keio Univ., Kanagawa, Japan

**Abstract:** The ability to flexibly switch between motor plans in response to changing environmental demands is essential for adaptive human behavior. This volitional motor reorganization is thought to involve cortical regions such as the pre-supplementary motor area (pre-SMA), right inferior frontal gyrus, and subthalamic nucleus. While previous neuroimaging work has established these areas' involvement, little is known about the temporal dynamics of switching-related neural activity, particularly as captured by scalp electroencephalography (EEG). The present study aimed to identify EEG-based spectral and spatial features that reflect individual differences in motor switching ability. Twenty-six healthy right-handed adults (mean age =  $22.1 \pm 1.3$  years; 10 females) completed a visually cued reaching task that required switching between two visuomotor mappings: a normal task (hand and cursor move congruently) and a mirror task (cursor movement inverted across the vertical axis). Each trial was categorized as either Stay (same mapping) or Switch (mapping alternation). Behavioral analysis revealed that reaction times (RTs) were significantly longer in Switch trials than Stay trials for both tasks (rmANOVA with post hoc t-tests,  $p = 0.010$ ,  $d = -0.36$ ;  $p = 0.023$ ,  $d = -0.39$ ), indicating successful induction of motor reorganization. EEG time-frequency analysis showed significantly increased theta-band (6-8 Hz) event-related spectral perturbation (ERSP) over the pre-SMA in Switch trials during early post-cue intervals ( $p < 0.05$ , paired t-test). Importantly, individual differences in theta ERSP magnitude were negatively correlated with Switch cost (RT difference between conditions; Pearson's  $r = -0.47$ ,  $p = 0.016$ ), suggesting that greater frontal theta power supports more efficient motor plan switching. These findings identify prefrontal theta oscillations as a non-invasive biomarker for volitional cognitive-motor flexibility. They further suggest that theta activity could be targeted in future neurofeedback or neuromodulation protocols designed to enhance adaptive motor control in both healthy and clinical populations.

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## **Poster**

### **PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.02/R14

**Topic:** F.04. Voluntary Movements

**Title:** Interaction between Model-based and Model-free Mechanisms in Motor Learning

**Authors:** \***A. D. KUMAR**<sup>1</sup>, **A. KUMAR**<sup>2</sup>, **N. KUMAR**<sup>1</sup>;

<sup>1</sup>Indian Inst. of Technology, Hyderabad, India, Sangareddy, India; <sup>2</sup>Queen's Univ., Kingston, ON, Canada

**Abstract:** Motor learning can be driven by distinct mechanisms—habitual, model-free processes, and strategic, model-based processes—depending on the magnitude and context of

movement errors. Although small and large errors are known to engage distinct motor learning mechanisms—model-free (implicit) or model-based (explicit), respectively—it remains unclear whether successfully deploying one mechanism might hamper the engagement of the other in subsequent learning tasks. Here, we investigated how prior engagement of a particular mechanism biases future adaptations, even when the new task context typically favours the alternative strategy. Across three experiments (N=82), participants performed reaching movements to targets that either remained fixed or “jumped” mid-movement by small (15°) or large (30°, 45°, or 60°) angles. When first exposed to small errors (15°), participants exhibited persistent aftereffects in subsequent catch trials and stable reaction times (RTs), hallmarks of a model-free, habitual process. Surprisingly, even when switching to larger error magnitudes later, these participants continued to show robust aftereffects and did not elevate RTs, indicating a carryover of model-free learning. Conversely, participants who initially experienced large errors showed minimal aftereffects and flexible RT modulation consistent with model-based strategies; this bias persisted in later sessions with smaller errors, leading to reduced habitual aftereffects. Notably, inserting a washout phase to reset baseline performance did not abolish these mechanistic biases, highlighting that the initial engagement of either model-free or model-based processes leaves a durable imprint on subsequent adaptations. Taken together, these findings demonstrate that motor learning is shaped not only by ongoing task demands (e.g., error magnitude) but also by an individual’s prior learning history. Understanding how initial learning experiences constrain future adaptations has broad implications for designing interventions and training protocols in motor rehabilitation and skill acquisition.

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## **Poster**

### **PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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**Topic:** F.04. Voluntary Movements

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**Title:** Parieto-motor laminar population dynamics during visuomotor integration and movement preparation

**Authors:** \*N. NANDI, L. LÓPEZ-GALDO, L. LOPES SANTIAGO, S. NOUGARET, B. E. KILAVIK;

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**Abstract:** Visually guided motor planning is crucial for generating goal-directed actions. There has been a shift from the traditional sequential model - where decision-making in parietal areas precedes motor planning, to a framework in which these processes occur simultaneously within a parieto-frontal network. In the first part of our work, we focused on macaque dorsal premotor cortex (PMd), and identified distinct neuronal populations, classified by their intrinsic timescales (short- and long- $\tau$ ). These two neural populations exhibited distinct movement preparation patterns. Recordings during a delay-match-to-sample arm-reaching task with a pre-GO delay, showed that both short- and long- $\tau$  neurons encoded the future movement direction during the preparatory period. However, this directional representation was more stable over the delay, as demonstrated by cross-temporal decoding, in the long- $\tau$  neurons. Additionally we observed that the preparatory end state, defined as the neural population-firing rate just before execution, emerged shortly after the matching cue, dissipated during viewing of visual distractors, and re-emerged before execution. Thus, this sub-population in PMd helps maintaining stability or reactivate memory during planning. We are now integrating this work into a more extensive project aimed at understanding how neural activity in PMd and parietal area 7a integrate visual input to form patterns transitioning into a preparatory state, to generate commands for arm-reaching movements. To this end, we are exploring a dataset recorded in a macaque implanted with custom-built chronic 3D multi-shank electrode arrays targeting four parieto-motor cortical areas (PMd, M1, 7a, and 5d). In our preliminary analysis of the expanded dataset, we found that the preparatory end state in PMd exhibited a temporal profile consistent with our earlier findings. Notably, in area 7a, the population activity during the pre-GO epoch, equivalent to preparatory end state in PMd, was directionally selective, despite the absence of visual input. This directional selectivity also existed during the matching cue presentation, suggesting that 7a reflects directionally tuned activity across distinct task epochs. In contrast, we did not observe a comparable directionally selective population state in M1 or 5d during the pre-GO period. Building on these findings, our ongoing work aims to further investigate the dynamics of movement planning in PMd and 7a and to determine whether these processes reflect parallel computation or coordinated interactions supported by directed information flow between them.

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## **Poster**

### **PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.04/R16

**Topic:** F.04. Voluntary Movements

**Support:** NSERC Alliance Grant 586022-2023

**Title:** Reaching with uncertainty during whole body movements

**Authors:** \*C. V. SEAVEY<sup>1</sup>, C. SEEDELKE<sup>4</sup>, D. F. COOKE<sup>2</sup>, T. HEED<sup>4</sup>, D. S. MARIGOLD<sup>3</sup>;  
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**Abstract:** We make countless movement-related decisions each day. However, these decisions are made in an environment that often changes, thus creating uncertainty. One method to study movement planning under uncertainty is the go-before-you-know paradigm. Participants must initiate movement towards potential targets before knowing which to touch, requiring them to decide where to move during ongoing action. Previous research shows that people direct their movement intermediately between multiple targets when uncertain about the final target (Chapman et al., *Cognition*, 2010). Even early in the reach, this differs from people who know which is the target. However, these findings are constrained to seated experiments consisting of short, rapid reaches. How does initiating a reach while walking, thus requiring full-body coordination, influence the reach strategy? In this situation, do reach trajectories still differ between conditions in which people are uncertain about the final target location compared to when they know its location in advance? In the present experiment, we instructed participants (Target N = 20; currently N = 8) to walk three steps and then reach and touch a cued target on a touchscreen. For each trial, we presented two potential targets and positioned their midline either to the left or right, resulting in four possible target locations. The touchscreen indicated which of the targets to touch (left or right) either before walking onset (immediate condition) or after walking onset, upon initiation of the reach (delay condition). To determine the initial reach strategy, we measured the angle of the finger trajectory from reach onset (release of a hip-mounted button) to 100 ms thereafter. We found a cue timing by target side interaction for the initial reach angle ( $p < 0.001$ ). When participants reached to the left targets (with the right hand), the initial reach angle differed between immediate ( $99.95 \pm 3.61^\circ$ ) and delay conditions ( $88.51 \pm 3.01^\circ$ ). However, cue timing did not affect the initial reach angle when participants reached towards the right targets (immediate =  $88.74 \pm 3.12^\circ$ , delay =  $88.96 \pm 3.25^\circ$ ). Results demonstrate that, during walking, reaching strategy differs when one initiates movement before versus after knowing where to direct their reach. Overall, this study provides an initial foundation to translate knowledge from highly controlled to more naturalistic environments.

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**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.05/S1

**Topic:** F.04. Voluntary Movements



**Support:** NIH Grant R01 NS134754

**Title:** Selective attention in motor working memory

**Authors:** \*T. MCCLURE<sup>1</sup>, H. HILLMAN<sup>2</sup>, S. D. MCDUGLE<sup>2</sup>;

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**Abstract:** Working Memory (WM) is a short-term store in which sensory and abstract information is maintained and manipulated. WM is thought to leverage domain-specific modules to hold different types of information (e.g., visuospatial or phonological) mostly independently from one another. The functional relationships between WM and other cognitive systems—like attention and long-term memory—is an active area of research. However, few studies have addressed how movement information is held in WM, known as motor WM. Our lab's prior research aimed to explore the nature of motor WM as a separate subsystem, demonstrating classic WM effects (e.g., primacy, recency, and limited capacity) in motor WM and providing evidence that non-somatosensory information related to recent movements is maintained independently from visuospatial WM. Building on this work, the present study examined the role of selective attention—the process by which relevant information is prioritized in order to guide behavior to serve ongoing goals—in motor WM. Prior research has investigated this using retro-cues, in which content is cued after it has been encoded in WM, and found that visuospatial information was recalled more quickly and accurately when retrospectively cued. These findings indicated that internally directed selective attention can prioritize content encoded in visuospatial WM. Here, we applied a similar approach in a motor WM task to determine whether selective attention can prioritize nonvisual movement information held within WM. Participants (N = 37) encoded a sequence of reaching movements without receiving any visual feedback, and, following some trials, were presented with a retro-cue indicating which of the movements from the sequence they would later recall. We found that an encoded movement was recalled more quickly and accurately when it was retrospectively cued, suggesting that selective attention can be directed within motor WM to select task-relevant content and to guide future action. Although previous studies have used retro-cues to explore the role of selective attention in different modalities such as auditory and tactile WM, to our knowledge, our study is the first to show that selective attention can be directed to nonvisual movement representations. These findings provide further evidence for a distinct motor WM module that, like other WM subsystems, is subject to internal modulation via selective attention.

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**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.06/S2

**Topic:** F.04. Voluntary Movements

**Support:** NSF (2133879)  
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**Title:** Ice is Nice: A Serious Game for Children Developing Upper Limb Prosthetic Control Skills

**Authors:** \*J. MCGINNIS<sup>1</sup>, L. ANDBERG KATZEN<sup>1</sup>, L. WONG<sup>1</sup>, J. SCHOFIELD<sup>2</sup>;  
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**Abstract:** Children with congenital limb differences have been shown to have the ability to consistently actuate their residual muscles to control advanced myoelectric prostheses. However, improving one's control over these assistive devices requires practice, which can become tedious and frustrating, especially when misclassifications disrupt visuo-motor congruence. This can lead to reduced motivation and loss of interest, which poses a significant challenge, as maintaining participant engagement is crucial for collecting high-quality data and improving training outcomes. To address this, we developed a serious game that provides an engaging way to practice actuating muscle groups relevant to myoelectric prosthetic control. "*Ice is Nice*" is a side-scrolling video game designed to address these challenges by prompting children to perform various movements with their missing hand, using the resulting classified biosignals as game input. By creating an immersive environment that promotes motor skill development and shifts one's focus of attention externally to be more outcome-oriented. The game receives real-time classifications from biosignals arising from muscle activity, while continuously logging data to capture metrics relevant to human motor learning, machine learning performance, and game proficiency. Our pilot work has evaluated the game's effectiveness in supporting motor learning compared to a traditional method using verbal prompts to guide forearm muscle contractions relevant to prosthetic control. We demonstrated that our system can integrate electromyography to control game play, performance metrics can be readily extracted, and *Ice is Nice* is generally perceived as a more enjoyable training experience. This game will serve as a platform for future studies involving children with congenital limb differences and take-home trials to explore the effects of motor learning on prosthesis use.

**Disclosures:** J. McGinnis: None. L. Andberg Katzen: None. L. Wong: None. J. Schofield: None.

## **Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.07/S3

**Topic:** F.04. Voluntary Movements

**Title:** Reach-like Neural Manifold Emerged in Ballistic Movements in Absence of Biomechanical Constraints

**Authors:** \*C. LI<sup>1</sup>, Q. WANG<sup>2</sup>, Y. ZHANG<sup>3</sup>, H. CUI<sup>1</sup>;

<sup>1</sup>Chinese Inst. for Brain Res., Beijing, China; <sup>2</sup>East China Normal Univ., Shanghai, China; <sup>3</sup>Inst. of Neuroscience, CAS, Shanghai, China

**Abstract:** Previous research demonstrated the preserved neural dynamics across animals performing similar behavior. To investigate the latent dynamics in motor cortex further, we adopted a predictive and two-dimension brain-controlled task that allowed to bypass the large degrees of freedom in neuromuscular systems. Being different from most neural decoding which relied on continuously converting neural activity to motor variables by fixed decoders and thus led to modest performance in speed and smoothness, our biomimetic decoding framework enabled monkeys to initiate neural states leading to a ballistic movement. In preparatory stage, a computer cursor was visually directed by motor cortical activity modulated by monkeys. Once the cursor touched the ring that surrounded the screen center, it was launched radially along a straight trajectory with a bell-shaped speed profile without in-flight correction. After implanting Utah arrays into their motor cortex, we trained two monkeys to intercept a moving target with circular velocity of  $\pm 120$  deg/s by the brain-controlled cursor. Within few weeks, both monkeys learned to utilize the decoder to launch the cursor, generating rapid interception of moving targets with a high success rate ( $>70\%$ ) and efficient trajectory. Strikingly, the preferred direction of neuronal tuning shifted across epochs, particularly before and after the cursor touched the ring (i.e., the preparatory and execution epochs). Dimensionality reduction revealed that population activity in brain-controlled trials resembled the dynamical structure observed in the manual interception. We analyzed population neuronal activity within 100 ms before and 300 ms after the ring-touch event by projecting it onto jPCA space. The neural trajectories exhibited a rotational structure, indicating the preserved neural dynamics in the brain control. Notably, only the correlations of the first three neural modes in the brain control was quite close to the correlations in the arm movement, and the aligned neural activities during arm reach provided an accurate prediction of brain-controlled ballistic direction. These preserved rotational neural dynamics emerging without biomechanical constraints may reflect intrinsic properties of motor cortex.

**Disclosures:** C. Li: None. Q. Wang: None. Y. Zhang: None. H. Cui: None.

**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.08/S4

**Topic:** F.04. Voluntary Movements

**Title:** Visuomotor Adaptation to Combined Rotation and Gain Reduction

**Authors:** R. N. ADDISON<sup>1</sup>, A. W. VAN GEMMERT<sup>2</sup>;

<sup>1</sup>Kinesiology, DePauw Univ., Greencastle, IN; <sup>2</sup>Col. of Human Sci. & Educ., Louisiana State Univ., Baton Rouge, LA

**Abstract:** Driven by sensory prediction errors, the nervous system is able to recalibrate motor commands in response to altered visual feedback, which is referred to as visuomotor adaptation. While directional rotations and gain perturbations have been studied independently, little is known about how the brain adapts to their combined effects. This study examined whether adding a reduction of gain alters adaptation to a 45° cursor rotation during a center-out reaching task. Twelve right-handed undergraduates (aged 18-22) used a stylus on a digitizing tablet while observing visual feedback on a screen. Two feedback conditions were tested in a counterbalanced order, separated by a 3-month washout: (1) rotation-only and (2) rotation + 0.5×gain. Each session included baseline, adaptation, and re-adaptation blocks. Initial direction error (IDE) was analyzed using Durbin's nonparametric tests and exponential decay modeling. T-test comparisons of fitted learning rates showed no significant differences between conditions across phases (baseline, early/late adaptation, aftereffect; all  $p > 0.32$ ), though mean trends suggested slower adaptation with the reduced gain. Durbin's tests revealed significant trial-wise IDE reduction during the rotation-only blocks, whereas no significant pairwise differences emerged for the combined rotation + gain condition, despite a significant omnibus effect. Re-adaptation was modest for both conditions but not statistically significant for the rotation only trials. These findings suggest that while compounded visual distortions may initially slow adaptation, they do not impede eventual recalibration. Results support internal model theories of motor learning and suggest shared mechanisms for integrating angular and amplitude errors—informing rehabilitation and interface designs that involve complex sensory transformations.

**Disclosures:** R.N. Addison: None. A.W. Van Gemmert: None.

## **Poster**

### **PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.09/S5

**Topic:** F.04. Voluntary Movements

**Support:** NIH R56GR1059824

**Title:** Testing the Effect of Hand Dominance on Arm Choice under a Movement Time Perturbation

**Authors:** \*T. SUBASH<sup>1</sup>, P. PIRAY<sup>2</sup>, N. SCHWEIGHOFER<sup>1</sup>;

<sup>1</sup>Biokinesiology and Physical Therapy, <sup>2</sup>Dept. of Psychology, USC, Los Angeles, CA

**Abstract:** Reaching movements post-stroke are variable, effortful, and slow. Prior work (Kim et al., 2022; Schweighofer et al., 2015) showed that paretic arm choice is influenced by success rates (variability), and physical effort. Here, we considered the potential impact of longer reaching movement time ( $MT$ ) on arm choice. The duration of fast movements, like eye saccades and arm reaches, acts as an implicit delay during reward acquisition (Berret & Baud-Bovy, 2022; Shadmehr et al., 2016). Previous research (Kim et al., 2022) suggests that in a

variable environment, dominant arm choice is more habitual than non-dominant arm choice. Therefore, we hypothesize that: 1.  $MT$  acts as a cost, reducing the likelihood of selecting the slower arm through temporal discounting. 2. Hand dominance affects how arm choice adapts to increased  $MT$ , with the dominant arm being more resistant to change due to stronger habitual preferences. Update of choice is slower when the  $MT$  is increased for the dominant arm than when the  $MT$  in the non-dominant arm is increased. We conducted an online Virtual Reality experiment to assess the effect of  $MT$  on arm choice. On each trial, participants were presented with two targets—one for each arm—varying in distance, size (per Fitts' Law), and angle to elicit a range of  $MT$ s. Participants chose one arm to reach its corresponding target, with the arms represented only by cursors. We modeled arm choice as a competition between action values assigned to each arm, which combine a reward discounted by  $MT$  and an effort term estimated using inverse dynamics. Using hierarchical Bayesian methods, we estimated the discounting rate ( $k$ ), reward-effort trade-off, choice randomness, and handedness bias. Data from right-handed, neurotypical participants show nearly equal selection of both arms before the perturbation. In separate groups, we perturbed either the dominant (right) or non-dominant (left) arm. Parameter estimation shows that  $MT$  affects decisions via a positive discounting parameter  $k$ , validated by parameter recovery, supporting our first hypothesis. Importantly, the rate of change in arm choice was higher when the non-dominant arm was perturbed, supporting our second hypothesis that dominant-arm choices are more resistant to change. These results highlight how movement time and hand dominance interact to affect arm choice and are relevant to understanding arm use post-stroke.

**Disclosures:** T. Subash: None. P. Piray: None. N. Schweighofer: None.

## **Poster**

### **PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR226.10/S6

**Topic:** F.04. Voluntary Movements

**Support:** NRF Grant No. 00450314  
NRF Grant No. 00209864  
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**Title:** Temporal Dynamics of Goal Representation and Information Flow Across DLPFC, PPC, and M1 During Online Goal Correction

**Authors:** \*M.-K. KIM<sup>1</sup>, S.-H. KIM<sup>2</sup>, H. PARK<sup>3</sup>, J.-W. SOHN<sup>4</sup>;

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<sup>2</sup>Intelligent Precision Healthcare Convergence, Sungkwunkwan Univ., Suwon, Korea, Republic of; <sup>3</sup>Catholic Kwandong Univ., Suwon-si, Korea, Republic of; <sup>4</sup>Med. Sci., Catholic Kwandong Univ., Incheon, Korea, Republic of

**Abstract:** Understanding how cortical circuits support rapid behavioral adaptation to unexpected changes in movement goals is critical for deciphering the neural basis of flexible behavior. In this study, we examined the functional roles and temporal dynamics of the dorsolateral prefrontal cortex (DLPFC), primary motor cortex (M1), and posterior parietal cortex (PPC) in non-human primates performing a center-out reaching task in which the target location was unpredictably changed during the movement, requiring online correction of reach trajectories. We addressed three key questions: (1) Which cortical area first exhibits changes in neural activity following an unexpected target change? (2) What are the precise temporal relationships among DLPFC, M1 and PPC during and after the correction? (3) How are predictive signals from DLPFC and sensory feedback from PPC integrated in M1 to update motor plans after a goal change? Single unit activity was recorded simultaneously from DLPFC, M1 and PPC. Analyses revealed distinct functional specializations: DLPFC neurons maintained and flexibly updated goal representations, M1 neurons were primarily involved in motor preparation and execution, and PPC neurons encoded spatial and attentional aspects of the changed target. To determine the temporal evolution of goal encoding, we trained classifiers to decode, at each time point, the direction of the initial target, the corrected target, and the difference between the two, based on the population activity in each area. For the initial target, decoding performance in DLPFC reached significance approximately 80 ms after target onset, while decoding in PPC and M1 became significant at around 120 ms and 150 ms, respectively. These results indicate that information about the updated goal emerges earliest in the DLPFC, followed by PPC and M1, revealing a clear temporal sequence across the network during online goal correction. Regarding the integration of predictive signals from DLPFC and sensory feedback from PPC in M1 during motor plan adjustment, further analyses are currently underway. These ongoing efforts employ cross-area decoding, neural trajectory analysis, and information-theoretic approaches to elucidate how M1 dynamically integrates top-down predictions and bottom-up sensory information in the context of rapid goal correction. Collectively, our findings provide a detailed temporal map of how DLPFC, PPC, and M1 contribute to flexible, goal-directed behavior and establish a framework for investigating the neural mechanisms underlying online behavioral adaptation to unexpected changes in goals.

**Disclosures:** M. Kim: None. S. Kim: None. H. Park: None. J. Sohn: None.

## **Poster**

### **PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.11/S7

**Topic:** F.04. Voluntary Movements

**Support:** Natural Sciences and Engineering Research Council of Canada Canada Graduate Scholarship - Doctoral  
Natural Sciences and Engineering Research Council of Canada Discovery Grant RGPIN-2025-04104

**Title:** Evidence of substantial improvements in computational efficiency of algorithmic strategies during sensorimotor learning

**Authors:** \*J. THOMAS<sup>1</sup>, H. E. KIM<sup>2</sup>;

<sup>1</sup>Univ. of British Columbia, Vancouver, BC, Canada; <sup>2</sup>Sch. of Kinesiology, The Univ. of British Columbia, Vancouver, BC, Canada

**Abstract:** Motor expertise relies on rapidly selecting actions based on goals and sensory input. With practice, selection moves from heavily deliberated and slow to effortless and rapid. This process, known as automatization, has been conceptualized as a move from deliberative (algorithmic) selection to strong stimulus-response associations (“response caching”; Haith & Krakauer, 2018; Logan, 1988), resembling a lookup table for actions. While response caching has empirical support (Hardwick et al., 2019; Huberdeau et al., 2019), recent data show that participants confronted with more stimuli than working memory capacity can handle (Miller, 1956) continue to use algorithmic selection (McDougle & Taylor, 2019), suggesting constraints on caching. There is evidence that cognitive algorithms such as mental rotation (Shepard & Metzler, 1973), which are known to be computed in simple sensorimotor tasks (Georgopoulos & Massey, 1987), can be accelerated with practice (Provost et al., 2013). Thus, we were motivated to test for substantial sensorimotor algorithmic efficiency improvements with practice. We conducted a study with explicit adaptation to visuomotor rotations, where cursor feedback related to the hand was rotated. McDougle & Taylor (2019) found only modest response time (RT) reductions after 300 trials for their 12-target condition, i.e., the condition that does not entail response caching due to excessive working memory demands. Here, we ran a two-day study (N = 5), where participants performed 1,440 trials with a 45° rotation applied to 12 targets. Feedback was delayed by 2 seconds to minimize implicit learning. Mean RTs declined from 658 ms at training start (SD 94; first 72 trials Day 1) to 475 ms after training (SD 63; last 72 trials Day 2), approaching the empirical floor in our task (Day 2 washout, 389 ms, SD 72) and RTs in McDougle & Taylor’s group that achieved automaticity. Task performance improved in parallel: reach angles rose from 30.56° (SD 8.12) at training start to 45.13° (SD 1.41) after training. These findings show that sensorimotor processing times can be substantially reduced when working memory is overburdened, without sacrificing accuracy. We conclude that algorithmic speeding is a viable alternative path to automaticity.

**Disclosures:** J. Thomas: None. H.E. Kim: None.

**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.12/S8

**Topic:** F.04. Voluntary Movements

**Support:** NIH-R37-HD087089  
NIH-R01-CRCNS-NS120579

**Title:** Hitting a target with a bullwhip: Internal models and their cognitive and physical determinants

**Authors:** \*A. KROTOV<sup>1</sup>, D. SKOTARCZAK<sup>2</sup>, D. STERNAD<sup>3</sup>;

<sup>1</sup>Bioengineering, Northeastern Univ., Boston, MA; <sup>2</sup>Northeastern Univ., New Providence, NJ;

<sup>3</sup>Departments of Biology, Electrical & Computer Engineering, and Physics, Northeastern Univ., Boston, MA

**Abstract:** It is widely understood that internal models of the body and the environment are necessary for controlling goal-directed movements. However, evidence for this concept has been mostly seen in highly simplified movements, such as reaching in the horizontal plane with systematic perturbations. In contrast, naturalistic movements involve interactions with various complex objects with many degrees of freedom and nonlinear internal dynamics, such as tying shoelaces. Recent studies suggested that humans exploit dynamic features of relatively simple physical systems, such as mass-springs or pendula. This study examines possible internal models - cognitive or embodied - underlying interactions with an exquisitely complex object: a bullwhip.

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Sixteen novices used a 1.6-m whip to hit a target at 2.2-m distance repetitively 150 times per day (with breaks). They practiced for 12 sessions over 4 weeks. Whole-body kinematics was recorded via 48 markers on the body, 18 on the whip and target. Prior to recording, all subjects completed a questionnaire evaluating their strength, stamina, and coordination, as well as sports experience. Half of the subjects were engineering majors and additionally completed a vibration-waves problem set and discussed a whip modeling paper and the whip action with the experimenter.

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With practice, all participants improved their target-hit rates from 5% to 35-60%. Correlations of cognitive understanding of whip behavior and athletic experience with hit rates showed that cognitive preparation did not predict performance success. While physical fitness also had no effect, experience with overarm sports, such as volleyball, positively correlated with performance.

-  
To further examine this ‘embodied’ knowledge, we formulated two physical models of the interactive dynamics and compared their features to experimental data: (1) Modeling the whip throw as launch of an imaginary ball from the hand, handle, and center of mass (CoM) of the whip explained the direction of release and spatial error for the ball released at the whip CoM, but not at the hand or handle. (2) Modeling the whip as a one-dimensional unfolding string explained the prevalent direction of the whip’s CoM towards the target, the propagation of whip curvature, flight time, and tension at the handle.

-  
These results suggest that the internal representation of interaction with the complex whip dynamics may derive from throw-related experience and intuition about handling a ball or a one-dimensional string. Instead of being explicitly acquired, these simple general models appear to be embodied and present a suitable simplification that the CNS may rely upon and exploit for motor control.

**Disclosures:** A. Krotov: None. D. Skotarczak: None. D. Sternad: None.

**Poster**



**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR226.13/S9

**Topic:** F.04. Voluntary Movements

**Support:** NIH Grant NS131552

**Title:** Algorithmic planning in force adaptation

**Authors:** \*H. KAN<sup>1</sup>, J. A. TAYLOR<sup>2</sup>;

<sup>2</sup>Psychology, <sup>1</sup>Princeton Univ., Princeton, NJ

**Abstract:** In visuomotor rotation tasks, the use of strategies has been shown to facilitate rapid learning but at the cost of additional cognitive effort: preparation time increases with the rotation angle of the cursor, echoing classic Shepard mental rotation (Shepard and Metzler, 1971; McDougale and Taylor, 2019). Recent work has reported the use of strategies in other forms of sensorimotor adaptation, such as in force fields (McDougale et al., 2015; Schween et al., 2020; Forano et al., 2022), but it is unclear if they incur the same cognitive cost as in visuomotor adaptation. Here we sought to determine if preparation time increases parametrically with perturbation magnitude in a center-out, force-field adaptation task. On the first trial of the pair, participants were instructed to observe the force field, while on the second trial of the pair, participants were instructed to counteract the force they had just experienced. Critically, on a fraction of these second trials, a force channel was applied to the movement, allowing an accurate measurement of the counteracting force applied by the participants. The force perturbations were counterbalanced in magnitude and direction such that learning could not accumulate over the course of the experiment. We found that participants reliably scaled their force production proportionally to the forces they experienced - a scaling effect not observed in studies using a single-trial design that elicits only implicit adaptation (Fine and Thoroughman, 2006). More importantly, the preparation time of the movement scales with participants' force production. This finding suggests that strategies in forcefield adaptation also involve an algorithmic and time-consuming planning process, analogous to the mental rotation-like process found in visuomotor adaptation.

**Disclosures:** H. Kan: None. J.A. Taylor: None.

**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR226.14/S10

**Topic:** F.04. Voluntary Movements

**Support:** NIH-R37-HD087089  
NIH-R01-CRCNS-NS120579

**Title:** Interaction of rhythmic and discrete control objectives in the manipulation of a complex object

**Authors:** \*D. STERNAD<sup>1</sup>, R. LOKESH<sup>2</sup>;

<sup>1</sup>Biology, Electrical and Computer Engineering, Physics, <sup>2</sup>Northeastern Univ., Boston, MA

**Abstract:** Skillful actions often involve switching between different control objectives. For example, when swirling a glass of wine, the primary goal of control is to bring the wine (internal degree of freedom) into a rhythmic circular motion. However, when bringing the glass to the mouth, the goal is to translate the glass itself from one location to another. Such transition of control objectives, here from a rhythmic to a discrete goal, and from a focus on internal to external degrees of freedom, is an essential feature of dexterous object manipulation. This study designed a novel experimental paradigm where subjects manipulated a cup with a ball rolling inside (akin to a glass of wine) on a horizontal plane. The task was implemented in a virtual setting, where the cup-and-ball movements were displayed on a screen in top-down view and subjects controlled the cup via a robotic manipulandum, which provided haptic feedback. The task was to rhythmically "swirl" the ball close to the rim of the cup while keeping the cup within a "home" circular region. An auditory cue then signalled subjects to translate the cup in a reach-like manner towards a target and resume the ball swirling at the target. As such, the task involved two transitions, one from rhythmic ball motion to discrete cup translation at home position, and the other from discrete cup translation back to rhythmic ball motion when arrived at the target position. We examined how control mechanisms associated with rhythmic (ball) rotations and discrete (cup) translation interacted, and how such transitions affected planning and execution of the cup translation as a goal-directed reach-like movement. The results showed that subjects initiated the transition from rhythmic to discrete movement by tuning to a certain phase of the ball rhythmic cycle, prior to and after the reach. More importantly, the duration of the reach was modulated by the ball rhythmic phase prior to reach initiation, showing a strong effect of the ball's cycle on the reach execution. Simulations of the task dynamics revealed that such modulation facilitated the smoothness of transitions between rhythmic and discrete movements. These observations indicated that the control mechanisms responsible for rhythmic and discrete movements were not separate and the parameters of the discrete reaching movement were strongly affected by certain characteristics of the rhythmic movement.

**Disclosures:** D. Sternad: None. R. Lokesh: None.

**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.15/S11

**Topic:** F.04. Voluntary Movements

**Support:** MIT–Novo Nordisk Artificial Intelligence Postdoctoral Fellows Program

**Title:** The influence of direction and redundancy in discrete planar reaching

**Authors:** \*J. LACHNER;

Brain and Cognitive Sciences, Mechanical Engin., MIT, Cambridge, MA

**Abstract:** Kinematically redundant motor systems present a fundamental question in neuroscience: how do humans select one movement strategy among infinite possibilities? Traditional studies often constrain the limb to two-dimensional models, allowing analytical solutions of arm configurations. However, such simplifications limit our understanding of how redundancy is resolved in more naturalistic settings. In this study, we investigate how movement direction and physical redundancy affect trajectory curvature during discrete planar reaching under varying levels of arm constraint. Participants performed reaching movements across seven spatially arranged targets in both forward and reverse directions, using their dominant and non-dominant arms. The task was performed under three experimental conditions that varied the level of arm support and movement restriction: standing, unconstrained sitting, and constrained reaching. Hand trajectories were recorded using a planar, low-inertia robotic interface, and markerless motion capture was performed to extract 3D upper-limb kinematics. An additional hypothesis we aim to explore is that, without physical constraints, subjects will use their abundant degrees of freedom to optimize manipulability. The resulting kinematic data were projected into a physics-informed simulation framework with an anatomically structured arm model. This allowed us to explore whether observed curvature patterns arise from biomechanical factors such as inertial coupling. Simulations enabled us to isolate mechanical effects from control strategies observed in recorded movements. For each reach, we computed Average Lateral Deviation (ALD), a quantitative measure of trajectory curvature, by comparing the actual movement path to a straight line between start and target points. Reversing movement direction consistently produced more curved and variable trajectories, particularly under unconstrained conditions. Forward movements exhibited lower ALD values, indicating straighter and more repeatable trajectories. These findings inform how healthy humans resolve kinematic redundancy and may guide the design of robotic-assisted upper-limb therapy after stroke.

**Disclosures:** J. Lachner: A. Employment/Salary (full or part-time): Massachusetts Institute of Technology.

## **Poster**

### **PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.16/S12

**Topic:** F.04. Voluntary Movements

**Support:** Grant NSF BCS 2216344

**Title:** Testing the Effect of Perturbation Schedule on Memory Formation in Visuomotor Adaptation

**Authors:** \*Y. LI<sup>1</sup>, Y. ZHANG<sup>2</sup>, H. MAI<sup>2</sup>, N. SCHWEIGHOFER<sup>3</sup>;

<sup>1</sup>Computer Science, Univ. of Southern California, Los Angeles, CA; <sup>2</sup>USC, Los Angeles, CA;

<sup>3</sup>Biokinesiology and Physical Therapy, Univ. Southern California, Los Angeles, CA

**Abstract:** Recent computational models propose that learning multiple motor skills is due to creating, selecting, and updating memories (Oh & Schweighofer, 2019; Heald et al., 2021). However, the conditions that lead to new memory formation are not well understood. Here, we tested how new memory formation in visuomotor adaptation is affected by perturbation magnitude, prior adaptation, and task congruency. Participants in eight groups (N = 10/group) completed a baseline block and three perturbation blocks (110 trials each), each separated by washouts (W, 170 trials). Perturbations were large (L = 30°), medium (M = 20°), opposite medium (M- = -20°), small (S = 10°), or null (N = 0°). We tested three hypotheses: 1. We first aimed to replicate the results of Oh & Schweighofer (2019). After experiencing an L block, participants formed a new memory, which manifests itself as savings when the L perturbation is reintroduced. In contrast, no savings followed an S perturbation. We compared learning in the two L blocks in Group 1 (L W N W L) and the two S blocks in Group 2 (S W N W S). 2. We adapted the design of Bond & Taylor (2017) to examine the savings in an M or M- block when preceded by an L or S block. Experiencing the L block creates a memory that is reactivated during the M block. By contrast, experiencing an S or N block does not induce a new memory - so learning in the M block must rely on creating a new memory. The same situation happens if the M block following the L block has the opposite sign (M-) since the previously formed memory in the L block cannot be reused. We compared learning in the M block of Group 3 (L W M W L) against the M and M- blocks in Group 4 (S W M W S), 5 (N W M W S), and 6 (L W M- W L), and predicted faster learning in Group 3. 3. Morehead et al. (2015) found that learning is faster in an M- block when it follows an L block than when it follows an S block. However, it remains unclear whether L exposure facilitates learning in M- or if S exposure hinders it. We hypothesized that L exposure creates a memory that is unused during the M- block, and S exposure does not form a new memory. However, as no memory was created during an S block, the baseline memory was affected by the S block and thus slowed the learning in the M-. We compared learning in the M- block of Group 6 (L W M- W L), 7 (S W M- W S), and 8 (N W M- W S) and predicted slower learning in Group 7. We fitted the adaptation results with a mixed-effect model and observed 1) Group 1 showed a higher learning rate in the second L block than in the first L block; 2) in the M(-) block, Group 3 adapted faster than Group 4, 5, and 6; 3) in the M- block, both Group 6 and 8 learnt faster than Group 7. Overall, our results align with our hypotheses and shed light on how adaptation processes and memory-formation mechanisms.

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**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR226.17/T1

**Topic:** F.04. Voluntary Movements

**Support:** NSF BCS 2216344

**Title:** De Novo Motor Skill Learning with a Reverse Tracking Task on Smartphones

**Authors:** \*H. MAI<sup>1</sup>, Y. LI<sup>2</sup>, N. SCHWEIGHOFER<sup>3</sup>;

<sup>1</sup>Computer Sci., USC, Los Angeles, CA; <sup>2</sup>Computer Science, Univ. of Southern California, Los Angeles, CA; <sup>3</sup>Biokinesiology and Physical Therapy, Univ. Southern California, Los Angeles, CA

**Abstract:** A previous study of learning to ride a reversed bicycle revealed that participants "unlearned" how to ride a traditional bicycle before learning how to ride the reversed bicycle. Evidence of this interference persists even after extensive practice (Magnard et al. 2024). Conversely, other studies on de novo motor learning revealed little interference after acquiring a new task (Haith et al. 2022). In addition, it has been proposed that motor skill acquisition is associated with an increase in the planning horizon (Bashfold et al. 2022). Our goal is to understand how performance and planning horizon evolve when human participants first learn a normal control task and then learn a reversed-mapping task. Participants were instructed to control a simulated ball by tilting a smartphone about its pitch and roll axes. The ball's vertical and horizontal velocities were proportional to the pitch and roll angles, respectively. In the reversed-mapping condition, the ball's movement along one or both tilt axes were inverted. The goal was to track a target moving at constant speed along a track defined by a sum of sinusoids of different frequencies. A preview of the forthcoming track was displayed for up to 2s. Each day of training comprised three types of blocks: 1. Training block: 10-minute practice with a 2s preview; 2. Short-testing block: 1-minute evaluation with a 2s preview; and 3. Horizon-testing block: 10-minute evaluation with ten 1-minute segments in which the preview varied from 0.2s to 2s. On day 1, participants performed normal short testing at the beginning and end of the experiment. Between these two blocks, they completed two normal training blocks, each of which was immediately followed by normal horizon testing. Beginning on Day 2, participants started both normal and reverse short testing, then switched to reverse mapping training. The two reverse training blocks were followed by reverse and normal horizon testing, respectively. Finally, another reverse short-testing was given. Our preliminary results indicate that participants could learn both normal and reversed tasks, as indicated by lower mean squared distance to the target and reduced power of the motor inputs across short-test blocks. However, performance was lower for the reversed task, especially at higher frequencies, and some degree of interference was present. The planning horizon increased for both the normal and reversed tasks with training. We interpret our results in light of modeling work showing that learning multiple motor skills requires both learning to predict and learning to control, with learning to control modulated via responsibility signals derived from predictions.

**Disclosures:** H. Mai: None. Y. Li: None. N. Schweighofer: None.

**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.18/T2

**Topic:** F.04. Voluntary Movements

**Support:** NIH R56GR1059824

**Title:** Individual Differences in Three Distinct Motor Learning Mechanisms in Humans

**Authors:** \*R. POUDEL<sup>1</sup>, H. MAI<sup>2</sup>, Y. ZHANG<sup>2</sup>, C. WINSTEIN<sup>1</sup>, N. SCHWEIGHOFER<sup>1</sup>;

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**Abstract:** Motor learning involves distinct mechanisms: cerebellar-dependent adaptation, motor cortex-mediated skill learning, and basal ganglia-linked reinforcement learning. Although individuals show large variability in each of these learning mechanisms, it is not well understood whether learning in one mechanism can predict or correlate with learning in the others. Previous studies have reported no correlation in implicit learning between adaptation and sequence learning tasks in young adults (Stark-Inbar et al., 2017). In contrast, another study has demonstrated a correlation in overall performance between adaptation and reinforcement learning (de Brouwer et al., 2022). We aimed to investigate individual differences and correlations among three motor learning mechanisms: 1) adaptation via a visuomotor rotation task, 2) skill learning via a mirrored star tracing task, and 3) reinforcement learning via a step reaching task, in a single group (N = 15). All participants completed the three tasks online, with at least a 1-week break between tasks, using their dominant hands on a laptop trackpad. The visuomotor rotation adaptation task, modified from Hadjiosif et al. (2023), involved reaching a 90-degree target with a 30-degree clockwise perturbation. The learning block included three one-minute breaks to allow explicit learning to decay, followed by no-feedback trials to assess implicit learning. The mirrored star tracing task, modified from Bootsma et al. (2021), required tracing a six-point star under vertical (left-right) mirror transformations. Performance was measured using a speed-accuracy trade-off metric combining speed and accuracy based on mean squared distance from the centerline. Interference was assessed by normal tracing after mirror tracing. The reinforcement learning task, modified from Zhu et al. (2023), involved discovering four hidden targets on four horizontal lines by trial and error, guided by a reward score feedback. Participants demonstrated learning across all three motor learning tasks. Initial analyses indicate large between-subject variability in all three tasks and a correlation between the explicit component of adaptation and the rate of reinforcement learning. Thus, our results show large between-subject differences for the same task and within-subject differences for different motor learning tasks. These results suggest that choosing the right type of motor learning task for each learner is important in both sports and rehabilitation.

**Disclosures:** R. Poudel: None. H. Mai: None. Y. Zhang: None. C. Winstein: None. N. Schweighofer: None.

**Poster**

**PSTR226: Reaching Control: Movement Psychophysics and Neurophysiology**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR226.19/T3

**Topic:** F.04. Voluntary Movements

**Support:** NIH R56 NS126748

**Title:** To learn or not to learn? Model-based estimation of motor learning from a large, "in the wild", home rehabilitation database

**Authors:** \*Y. WEN<sup>1</sup>, D. YE<sup>1</sup>, R. POUDEL<sup>1</sup>, D. J. REINKENSMEYER<sup>2</sup>, D. ZONDERVAN<sup>3</sup>, N. SCHWEIGHOFER<sup>4</sup>;

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**Abstract:** Motor learning—a set of internal processes associated with practice or experience leading to relatively permanent changes in skilled behavior (Schmidt et al., 2019)—is critical for regaining motor function following brain injury (Krakauer et al., 2019). However, quantifying learning in real-world, unsupervised settings remains challenging. Here, we present a model-based framework to estimate the presence and, if applicable, the extent of motor learning across multiple tasks and users from a large “in-the-wild” rehabilitation dataset collected via FitMi, a home rehabilitation device. We analyzed 4,661 episodes—each consisting of repeated sessions for one user and one task—from 398 FitMi users practicing various combinations of 20 upper-limb tasks for at least 50 sessions. For each episode, we modeled the effect of daily dose (input: number of repetitions) on performance (output: repetitions per second) using a discrete-time first-order state-space model, where latent motor memory evolves with cumulative practice. The key parameters were the learning rate, which governs memory updates given input dose, and the forgetting time constant, which controls memory decay. Parameters were estimated using the Expectation-Maximization (EM) algorithm with Kalman smoothing (Albert & Shadmehr, 2018). Simulation-based parameter recovery using estimated parameters and actual inputs confirmed robust estimation despite realistic noise and variability. We then used a likelihood ratio test (LRT) to compare this learning model to a non-learning (performance-only) model, classifying each episode as “learning” or “non-learning”. Overall, 38.3% of episodes were classified as learning. Among these, 44.6% had significantly long time constants (> 30 days), indicating durable motor memory. In contrast, non-learning episodes displayed short time constants (< 2 days), reflecting transient performance fluctuations. Learning episodes also involved more frequent and sustained sessions. Task-level analysis revealed no clear dichotomy between learnable and non-learnable tasks. Among users who practiced at least 5 tasks, 18% were non-learners, ~ 5% learned all tasks, and the rest exhibited a mix of learning and non-learning across tasks. Our findings demonstrate that real-world rehabilitation induces motor learning—at least in some tasks and users—detectable through computational modeling. Future work will incorporate user-level covariates and hierarchical Bayesian models to better characterize population-level learning dynamics. Our results have implications for optimizing post-stroke rehabilitation through individualized task selection.

**Disclosures:** Y. Wen: None. D. Ye: None. R. Poudel: None. D.J. Reinkensmeyer: None. D. Zondervan: None. N. Schweighofer: None.

**Poster**

**PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.01/T4

**Topic:** F.06. Posture and Gait

**Title:** Predicting Walking Terrains Using Machine Learning and Predictions of Body-Worn Sensor Signals

**Authors:** \*S. JONES<sup>1</sup>, G. SIMPSON<sup>2</sup>, P. M. PILARSKI<sup>4</sup>, A. DALRYMPLE<sup>3</sup>;

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**Abstract:** Lower-limb exoskeletons have the potential to aid in the rehabilitation of walking for individuals who have suffered a variety of neuromuscular deficits, including stroke and spinal cord injury. Day-to-day community ambulation requires the ability to modify walking to adapt to the environment and walking terrain. However, current exoskeleton controllers rely on manual input to switch modes for different terrains (e.g. stairs), limiting their effectiveness in real-world use. To address this, we propose an adaptive control strategy using Hierarchical Reinforcement Learning (HRL), which decomposes complex tasks into simpler, adaptable sub-tasks. Hierarchical control is inspired by the learning and control processes of the dorsolateral prefrontal cortex. Our approach employs HRL to reduce the control problem into two components: 1) a lower-level framework that provides predictive information of lower-limb sensor signals in the form of general value functions (GVFs) to inform higher-level decision making, and 2) a higher-level framework that adaptively predicts the walking terrain. We specifically investigate whether it is more effective to integrate predictions of sensor signals into the input layer versus the latent space in the higher-level framework. Ten participants walked over varied terrains, including even and uneven ground, stairs, ramps, and turns while wearing a suite of sensors, including electromyography (EMG), goniometers, and pressure-sensing insoles. GVFs were learned to predict lower-limb sensor signals 0.5 seconds into the future using True Online Temporal-Difference Learning (TOTD). We compared three policy networks for classifying terrain, one using GVFs at the input layer, one integrating GVFs into the latent space, and a control network without GVFs. Both GVF-integrated networks significantly outperformed the control network's 66.9% accuracy in comprehensive terrain classification, with improvements of 6.8% for the input layer network and 4.7% for the latent space network. However, there were no significant differences between the two GVF integration methods. GVF-integrated networks improved classification accuracy for terrains commonly misclassified by the control network, which includes even ground, uneven ground, up and down ramps, and turns.



These findings suggest that incorporating predictive sensor information enhances terrain classification, potentially enabling autonomous switching of control strategies for assistive devices.

**Disclosures:** S. Jones: None. G. Simpson: None. P.M. Pilarski: None. A. Dalrymple: None.

## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.02/T5

**Topic:** F.06. Posture and Gait

**Title:** Early muscle activation in gait after a self-mobilization exercise program: preliminary study

**Authors:** \*D. SHIBATA, Y. YOSHIDA;  
Univ. of New Mexico, Albuquerque, NM

**Abstract:** The integration of multisensory signals is crucial for maintaining postural stability and coordinating muscle activities. A self-mobilization exercise program was developed to realign spinal curvature, resulting in decreased postural sway in static standing and optimized trunk-hip kinematics without changes in kinetics during gait. However, the coordination of muscle activities during gait in response to postural correction by the exercise program is unknown. Thus, this preliminary study aims to examine whether muscle activations in electromyography (EMG) during gait would be altered based on these adaptations. Twenty-eight healthy young adults were randomly assigned to either the Exercise (Ex: n=14) or Control group (Ctrl: n=14). The Ex group performed three warm-up positions and seven small movements while lying on a cylindrical tube (98cm length, 15cm diameter). The Ctrl group laid supine on a flat surface with their hips and legs flexed. The duration of the respective interventions for both groups was 15 min. Before and immediately after the interventions, subjects walked on an 11.8m path for 8 trials at a comfortable speed. Embedded force plates (AMTI, Inc.) were used to detect the heel strikes and compute the gait cycle. Muscle activations of the vastus lateralis, biceps femoris, tibialis anterior, and gastrocnemius of both limbs were recorded with surface EMG (Trigno™ Wireless, Delsys, Inc.). Amplitude of EMG was normalized to the peak activity during the maximum voluntary isometric contractions. The signals are time-normalized over 100 frames for one gait cycle. Thus, the timing of peak activation was expressed as a percentage of one gait cycle from heel strike. ANCOVAs, with pretest measures as the covariate, were used to examine differences in the timing of peak activation between the groups after the interventions. No significant differences were found in Ctrl group ( $p > 0.05$ ). The Ex group showed a significantly earlier peak activation in the gastrocnemius and vastus lateralis of the right limb only after the exercise program ( $p < 0.05$ ). This finding can be interpreted as immediate adaptations to these kinematic changes using feedforward control. Fast walking generally decreases the stance phase

and induces earlier muscle activations during the loading response. The decreased stance phase of the left limb, found in our previous study, might result in the detention of earlier muscle activations of the right limb. To better understand the coordination of muscle activation, we currently investigate areas under the curve of EMG as an indication of the magnitude of muscle activity.

**Disclosures:** D. Shibata: None. Y. Yoshida: None.

## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.03/T6

**Topic:** F.06. Posture and Gait

**Title:** Optimizing sensor placement for terrain prediction during walking

**Authors:** \*W. YOUNG<sup>1</sup>, G. SIMPSON<sup>4</sup>, S. JONES<sup>2</sup>, K. NORTH<sup>2</sup>, P. M. PILARSKI<sup>5</sup>, A. DALRYMPLE<sup>3</sup>;

<sup>1</sup>Dept. of Biomed. Engin., <sup>3</sup>Biomed. Engin., <sup>2</sup>Univ. of Utah, Salt Lake City, UT; <sup>4</sup>Univ. of Utah, Dept. of Biomed. Engin., Salt Lake, UT; <sup>5</sup>Univ. of Alberta / Alberta Machine Intelligence Inst., Edmonton, AB, Canada

**Abstract:** Assistive devices for rehabilitation must adapt to diverse terrains using information about the environment, which can be conveyed using signals from body-worn sensors that measure muscle activity or limb movement. Machine learning can enable terrain classification, but excessive body-worn sensors can be impractical for daily use with assistive devices. Optimizing sensor type and placement is essential for accurate, low-burden rehabilitation systems. This study utilized Shapley Additive Explanation (SHAP) analysis to identify the most influential features of sensor signals for terrain classification, refining sensor selection while also providing insight into biomechanical adaptations to different terrains. Ten healthy participants (3 female; 19 - 31 years of age) were instrumented with electromyography (EMG) sensors bilaterally on the Lateral Gastrocnemius (LG), Vastus Lateralis (VL), Biceps Femoris (BF), and Tibialis Anterior (TA) muscles, along with pressure-sensing insoles placed in both shoes. Participants walked over varied terrains including even and uneven ground, up and down stairs, and up and down ramps. Sensor data were segmented into complete gait cycles, and 133 temporal, spectral, and spatial features were extracted. Terrains were classified using multi-kernel learning via support vector machines (SVMs). SHAP analysis informed feature reduction based on each feature's impact on model output. An ensemble of seven one-vs-all SVMs was trained to classify terrains from an unseen step. SHAP analysis revealed sensors that contributed minimally and maximally to terrain classification. BF was crucial for down ramp classification, but was the least used sensor overall, while the LG was the most frequently used to classify all terrains. Among pressure regions, rearfoot lateral and forefoot toe contributed the least, whereas

the rearfoot medial region was the most utilized in terrain classification. This suggests that BF plays a key role in downhill stabilization, while LG and rearfoot medial sensors consistently contribute to multiple terrain classifications, reflecting their important role in gait overall. Regarding individual terrain classifiers, the ramp ascent classifier had the lowest F1-score (0.77), indicating gaps in sensor information for this terrain. The down stairs ( $F1 = 0.91$ ) and uneven ground ( $F1 = 0.92$ ) classifiers performed best. These results highlight the importance of optimizing sensor placements and features to accurately predict different terrains, supporting more efficient sensor configurations for future control of assistive devices.

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## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.04/T7

**Topic:** F.06. Posture and Gait

**Title:** Estimating Ground Reaction Force Waveforms from Shank-Mounted Inertial Measurement Unit Using Bidirectional LSTMs

**Authors:** \*K. NORTH<sup>1</sup>, C. ANDERSEN<sup>1</sup>, G. M. SIMPSON<sup>2</sup>, S. T. JONES<sup>1</sup>, W. YOUNG<sup>3</sup>, A. N. DALRYMPLE<sup>1</sup>;

<sup>1</sup>Biomed. Engin., Univ. of Utah, Salt Lake City, UT; <sup>2</sup>Biomed. Engin., Univ. of Utah, Dept. of Biomed. Engin., Salt Lake, UT; <sup>3</sup>Dept. of Biomed. Engin. Univ. of Utah, Salt Lake City, UT.

**Abstract:** Gait is profoundly affected by neurological impairment. Ground reaction forces (GRFs) provide detailed insight into these deficits, reflecting the coordination and strength of muscles and joints throughout the stance phase. However, direct GRF measurement typically requires force plates or pressure-sensing insoles, both of which are expensive, lab-constrained, or unsuitable for long-term monitoring. In contrast, inertial measurement units (IMUs) are low-cost, robust, and suitable for continuous, real-world data collection. We hypothesized that acceleration data from a single shank-mounted IMU could be used to reconstruct vertical GRFs using deep learning, enabling accessible estimation of biomechanical load during gait. Ten healthy participants (3 female, mean age  $24.7 \pm 3.4$  years) walked at self-selected speeds over a flat indoor surface while instrumented with IMUs affixed to the belly of the tibialis anterior and pressure-sensing insoles in both shoes. Each trial lasted between 78 and 120 seconds. Data from each trail were segmented into 13-second windows, generating six datasets per trial and totaling 60 datasets across participants. We developed a deep learning model to estimate continuous GRF waveforms from triaxial accelerometer input. The sequential data was passed through a bidirectional long short-term memory (BiLSTM) network with a hyperbolic tangent (tanh) activation function. This architecture allows the model to preserve temporal context in both

forward and reverse directions, learning spatial-temporal patterns throughout the gait cycle. The BiLSTM outputs were averaged and passed through a three-layer multilayer perceptron (MLP) with 128, 384, and 320 nodes using rectified linear unit (ReLU) activations, producing frame-by-frame GRF predictions. An 80/20 train-test split was applied. Model performance was evaluated using root mean squared error (RMSE) and relative RMSE (rRMSE), comparing predicted and measured GRFs normalized to body weight. The model achieved an average RMSE of  $0.18 \pm 0.05$  % body weight and an average rRMSE of  $25 \pm 7.5\%$  across subjects. Predicted GRFs closely matched measured waveforms in both amplitude and timing throughout stance. These results demonstrate that wearable IMUs combined with a BiLSTM-MLP model can accurately reconstruct GRFs in a low-resource, portable setup. This approach enables GRF estimation outside of laboratory settings and may support remote gait monitoring in individuals with motor deficits. By enabling longitudinal and low-resource assessment of functional load-bearing, this tool could enhance evaluation and personalization of neurorehabilitation.

**Disclosures:** K. North: None. C. Andersen: None. G.M. Simpson: None. S.T. Jones: None. A.N. Dalrymple: None.

## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.05/T8

**Topic:** F.06. Posture and Gait

**Support:** Department of Physical Medicine and Rehabilitation Pilot Grant

**Title:** Don't be Trippin': Understanding the Biomechanics of Walking Across Different Terrains

**Authors:** \*G. SIMPSON<sup>1</sup>, K. NORTH<sup>2</sup>, S. JONES<sup>2</sup>, W. YOUNG<sup>4</sup>, P. M. PILARSKI<sup>5</sup>, A. DALRYMPLE<sup>3</sup>;

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**Abstract:** Spinal cord stimulation and lower-limb exoskeletons are methods for providing rehabilitative assistance for individuals with motor impairments, such as after stroke or spinal cord injury. Current assistive devices struggle to provide assistance over the variety of terrains people will encounter in their daily lives while walking around their community. Daily ambulation in the real world includes multiple types of terrain such as even ground, uneven ground, slopes, and stairs. How people subtly adjust their gait with a change in terrain to maintain stability is not well understood. To address this gap, we performed biomechanical analyses to understand how people's gait differs while walking on different terrains. Here, we examine the biomechanical differences in the lower limbs while people walked across

different terrains. In 10 neurologically-intact individuals (3 female,  $24.7 \pm 3.2$  years of age), we recorded lower-limb muscle activity using electromyography (EMG), joint angles from goniometers, and underfoot pressure from insoles as they walked across even ground, uneven ground, stairs, and ramps. From these body-worn sensors, we extracted 441 temporal, spatial, and spectral attributes from the gait cycles at steady state for each terrain. Steady state was defined as the steps on a terrain excluding the first 2 and last 2 steps after and before a transition, respectively. Attributes include metrics such as the stance phase variance, swing phase variance, and area under the curve for stance and swing phase for the EMG. We used principal component analysis (PCA) on the multi-terrain dataset to find which attributes contributed most to the variance to reduce the 441 attributes down to a set without multicollinearity.

The first three principal components of the PCA explained 47%, 37%, and 8% of the variance, respectively, for even ground ( $n = 489$  steps) and upstairs ( $n = 489$  steps) terrain data. The third temporal component of the vastus lateralis EMG during swing phase had the strongest correlation with principal component one (0.95). The central frequency variance for the vastus lateralis EMG during stance phase had the strongest correlation with principal component two (0.96). The third temporal moment of the biceps femoris EMG during swing phase had the strongest correlation with the third temporal moment (0.97).

Future work will also focus on the transitions between different terrains. Collectively, these findings will provide the groundwork for developing adaptive control strategies that enable individuals with motor impairments to ambulate in their community safely and confidently.

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## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.06/T9

**Topic:** F.06. Posture and Gait

**Title:** Ankle Position Sense Acuity is Higher in Plantarflexion than in Dorsiflexion

**Authors:** Y.-T. LEE<sup>1</sup>, F. MIRBAGHERI<sup>2</sup>, \*X. ZHOU<sup>3</sup>, J. KONCZAK<sup>3</sup>;

<sup>2</sup>Biomed. Engin., <sup>3</sup>Kinesiology, <sup>1</sup>Univ. of Minnesota, Minneapolis, MN

**Abstract:** Intact ankle proprioception is essential for the control of balance and gait. The main rotation of the ankle during standing balance and gait occurs in the sagittal plane, that is, towards plantar- or dorsiflexion. Whether the proprioceptive acuity differs for these main ankle positions is unknown. This study determined ankle position sense acuity for plantarflexion and dorsiflexion. In two separate assessments, the right ankle of 30 healthy young adults was passively rotated from neutral joint position to a 15° reference position and a smaller comparison position in either plantar- or dorsiflexion. Subsequently, participants verbally indicated which

position felt more flexed. After 25 trials, a psychometric function was fitted to the respective response-stimulus size difference data for each participant and two outcome measures were derived: a Just-Noticeable-Difference (JND) threshold as a measure of systematic error and an Uncertainty Area (UA) indicating random error. Analysis showed that mean JND threshold and median UA were both significantly higher in dorsiflexion when compared to plantarflexion ( $p = 0.008$ ,  $d = 0.52$ ;  $p = 0.001$ ,  $r_b = 0.58$ ). These findings indicate that ankle proprioceptive acuity is not uniform for sagittal plane ankle motion but is higher for plantarflexion. Possible reasons for this direction-specific acuity may be due to differences in plantar- vs. dorsiflexor muscle mechanoreceptor density and/or differences in central processing of proprioceptive signals. The findings highlight the importance of understanding movement-specific proprioceptive acuity for designing effective rehabilitation protocols.

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## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.07/T10

**Topic:** F.06. Posture and Gait

**Support:** 1R35NS122266 to AJB

**Title:** Development of Reinforcement Motor Learning of Locomotion

**Authors:** \*N. B. CASTLE<sup>1</sup>, H. TRIPP<sup>3</sup>, C. ROSSI<sup>2</sup>, A. J. BASTIAN<sup>4</sup>;

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**Abstract:** During learning, many locomotor patterns may be explored to find one that best accounts for new situations. Consider a child learning to walk in rain boots for the first time. They will explore different stepping patterns to learn the one that leads to stable footing. Here, we tested whether there is a developmental time course of reinforcement learning as children learned new walking patterns. Children aged 7-18 walked on a treadmill under 3 conditions: (1) baseline to establish preferred walking patterns (no target, no feedback), (2) visually targeted stepping to establish if they can use visual feedback of their step lengths to hit a visual target, and (3) reinforcement learning where they did not have visual targets and had to explore to find the pattern that would lead to success (fireworks on the screen). We quantified how variable children's stepping patterns were at baseline and measured success rates as well as exploration patterns during the visually targeted and reinforcement learning conditions. Results showed that, at baseline, stepping variability was highest for younger children and gradually improved (reduced) with age. This may reflect motor noise in younger children's motor performance as has

been previously suggested. We also found a clear relationship between a child's age and the percentage of successful steps that they took during the visually targeted stepping condition and the reinforcement learning condition. We are currently exploring if baseline variability and exploration patterns differentially affect these abilities during development.

**Disclosures:** N.B. Castle: None. H. Tripp: None. C. Rossi: None. A.J. Bastian: None.

## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.08/T11

**Topic:** F.06. Posture and Gait

**Support:** 1R35NS122266

**Title:** Boosting locomotor propulsion through adaptation and reinforcement learning

**Authors:** \*A. CASTRO E COSTA<sup>1</sup>, A. J. BASTIAN<sup>2</sup>;

<sup>1</sup>Neurosci., Kennedy Krieger Institute, Johns Hopkins Sch. of Med., Baltimore, MD; <sup>2</sup>KKI / Johns Hopkins, Baltimore, MD

**Abstract:** Locomotion is an automatic skill acquired in childhood. Once established, walking patterns can be difficult to change because they become deeply ingrained and automatic. Yet, after injury, people often need to learn a new walking pattern to improve symmetry, stability, and energy cost. Here, we tested whether healthy adults could learn a novel walking pattern using two visuomotor tasks: adaptation driven by error-based feedback or reinforcement driven by binary feedback. Both tasks were designed to help subjects learn to increase one leg's propulsive forces exerted on the ground at the end of stance to aid advancement of that leg during swing. This was done to understand how to address unilateral leg control deficits, which are a common deficit observed in people with cerebral palsy and stroke. Subjects walked on an instrumented treadmill (Motek M-Gait) and performed error-based or reinforcement-based tasks on different days in a randomized order. Both tasks involved equivalent locomotor demands but used different visual feedback signals driving learning. Results thus far show that adults can learn to increase propulsive forces in the trained leg using either error or reinforcement feedback. Braking forces also increased on the opposite leg during weight transition, demonstrating appropriate inter-limb coordination. Learning in both tasks also involved alterations in the spatial and temporal control of one leg relative to the other, although there appears to be some variability in the coordination pattern selected by different individuals. We are currently exploring whether there are differences in the amount of learning and retention between the two tasks. In sum, adults can learn new propulsive patterns during walking using adaptation and reinforcement learning mechanisms. Our goal is to expand this work to children with and

without cerebral palsy as a potential therapeutic tool targeting patient-specific locomotor impairments.

**Disclosures:** A. Castro e Costa: None. A.J. Bastian: None.

## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.09/T12

**Topic:** F.06. Posture and Gait

**Title:** Movement-specific fatigue score using m-space analysis correlates with self-reported rating of fatigue in a cross-modality ice dance fatigue paradigm of movement degeneration

**Authors:** \*N. S. YING<sup>1</sup>, S. G. YING<sup>2</sup>, A. G. YING<sup>6</sup>, Y. TARUI<sup>3</sup>, A. JOYCE<sup>7</sup>, A. JOYCE<sup>4</sup>, V. YE<sup>5</sup>, C. JOYCE<sup>7</sup>, M. BRAMANTE<sup>8</sup>, S. H. YING<sup>9</sup>;

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<sup>3</sup>Deeper Edge, Newton, MA; <sup>4</sup>Deeper Edge, Mansfield, MA; <sup>5</sup>Deeper Edge, Westwood, MA;

<sup>6</sup>DeeperEdge, Cambridge, MA; <sup>7</sup>DeeperEdge, Mansfield, MA; <sup>8</sup>Cambridge Col., Boston, MA;

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**Abstract:** BACKGROUND: An objective and quantifiable method that can accurately measure and rate movements is needed for clinical management and clinical trials. We previously demonstrated the use of m-space mapping to track progression of movement degeneration in a fatigue-inducing paradigm during ice dance, creating a movement-specific fatigue score (MSFS). Now, we test the hypothesis that MSFS correlates with self-reported rating of fatigue (ROF) scale, an emergent patient-reported outcome (PRO) measure used in disparate conditions. METHODS: The Dutch Waltz is a stereotyped ice dance pattern with eight step movements. 13 sets of 10 patterns of the Dutch Waltz were performed off the ice, and movements were measured using Rokoko inertial measurement unit sensors with full body coverage. Data were projected into m-space; principal component coordinates were used to calculate a MSFS for each movement. Non-fatigue vs fatigue trials were compared using Student's T-test. ROF scores (scale 0-10; 10=most fatigue) were compared to MSFS for each movement using Pearson's R coefficient. RESULTS: MSFS for individual steps for non-fatigue trials ranged from 26.9 to 42.6, mean +/- SD, 32.6 +/- 4.69 and for fatigue trials ranged from 53.3 to 60.3, mean +/- SD, 57.7 +/- 11.2. Individual step- and averaged step-specific MSFS differed ( $p < 0.004$  for individual,  $p < 0.00001$  for averaged) between non-fatigue (4 sets) and fatigue trials (9 sets). Self-reported ROF scores after each set varied between 2 and 6, mean 3.76. Average MSFS for an individual movement across a set correlated with ROF for most individual movements (Pearson's R range 0.11-0.91, median 0.81) as well as for overall average of MSFS across a pattern ( $R = 0.88$ ,  $p < 0.0001$ ). CONCLUSION: Movement-specific fatigue score (MSFS) correlated with self-reported rating of fatigue (ROF) for subjects performing Dutch Waltz movements off the ice. We



have previously shown that locations in m-space coordinates correspond to movement quality for an individual. As changes in m-space coordinates, represented by changes in MSFS, correlate with clinically important outcome measures, ROF, for movements off the ice, m-space mapping merits further investigation as a movement degeneration metric.

**Disclosures:** N.S. Ying: None. S.G. Ying: None. A.G. Ying: None. Y. Tarui: None. A. Joyce: None. A. Joyce: None. V. Ye: None. C. Joyce: None. M. Bramante: None. S.H. Ying: None.

## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.10/T13

**Topic:** F.06. Posture and Gait

**Title:** Functional electrical stimulation-induced ankle muscle co-contraction increases postural sway via elevated joint stiffness

**Authors:** \*F. SHOMAL ZADEH<sup>1</sup>, N. KUMAR<sup>2</sup>, J. W. LEE<sup>3</sup>, D. LIM<sup>1</sup>, J. LEE<sup>4</sup>, D. KUMBHARE<sup>1</sup>, K. MASANI<sup>1</sup>;

<sup>1</sup>KITE Res. Inst., Univ. Hlth. Network, Toronto, ON, Canada; <sup>2</sup>Computer Sci., Univ. of Toronto, Toronto, ON, Canada; <sup>3</sup>Oregon Hlth. & Sci. Univ., Univ. of Portland, Portland, OR; <sup>4</sup>Surgery, St. Michael's Hosp., Toronto, ON, Canada

**Abstract:** Individuals with incomplete spinal cord injury (iSCI) experience significant balance deficits during quiet standing due to weakness in ankle muscles—particularly the soleus (SOL) and tibialis anterior (TA)—which are critical for postural control. These individuals often develop compensatory co-contraction of these antagonistic muscles. While commonly viewed as a stabilizing strategy, our prior computational study suggested that this co-contraction may actually increase postural sway. This study aimed to experimentally investigate how ankle muscle co-contraction (SOL and TA), artificially induced by functional electrical stimulation (FES), affects postural sway through changes in ankle muscles and joint mechanics. First, we examined how FES-induced muscle contraction modulates ankle muscle stiffness and joint torque. Thirteen able-bodied adults participated in a supine protocol using an isometric dynamometer. Ankle joint torque and stiffness of the SOL and TA were measured across four conditions: rest, voluntary contraction, FES alone, and combined FES plus voluntary contraction, each at multiple intensities. Ankle muscle stiffness was quantified using ultrasound shear wave elastography (SWE) images. We observed strong linear correlations between ankle muscle stiffness and joint torque ( $r = 0.83-0.99$ ,  $R^2 = 0.93-0.98$ ), and a sigmoidal dose-response to FES intensity ( $R^2 = 0.94-0.99$ ). Notably, FES superimposed on voluntary contraction further increased stiffness and torque. Next, we tested how induced ankle muscle stiffness influences ankle joint quasi-stiffness and postural sway during standing. Five participants performed quiet standing trials on a force plate while receiving FES to the ankle muscles at varying intensities based on the dose-response

identified in Experiment 1. Simultaneous measurements included ankle muscle stiffness (via SWE images), joint quasi-stiffness (based on center of mass [COM] angle and ankle torque), and postural sway (COM acceleration). Results showed that increased co-contraction elevated both ankle muscles (SOL:  $R^2 = 0.94-0.99$ , TA:  $R^2 = 0.90-0.99$ ) and joint quasi-stiffness ( $r = 0.64-0.95$ ,  $R^2 = 0.60-0.91$ ), which in turn positively correlated with greater postural sway (COM acceleration:  $r = 0.92-0.99$ ,  $R^2 = 0.85-0.99$ ). These findings provide the first experimental validation that excessive ankle muscle co-contraction can increase postural sway, contrary to the common assumption that ankle joint stiffness enhances balance. This counterintuitive result underscores the need to optimize—not maximize—muscle activation strategies when using FES for postural rehabilitation in iSCI.

**Disclosures:** F. Shomal Zadeh: None. N. Kumar: None. J.W. Lee: None. D. Lim: None. J. Lee: None. D. Kumbhare: None. K. Masani: None.

## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.11/T14

**Topic:** F.06. Posture and Gait

**Support:** NIH 1P41EB018783  
VA Merit Award 01 CX001812  
New York State Spinal Cord Injury Research Board (SCIRB) C32236GG & C33279GG  
Stratton VA Medical Center, Albany, NY

**Title:** Locomotor Skill Acquisition Through Repeated Adaptations to Bi-directional Walking on a Split-belt Treadmill

**Authors:** \*H. MOJTABAVI<sup>1</sup>, R. L. HARDESTY, Jr.<sup>2</sup>, D. GUPTA<sup>4</sup>, J. WOLPAW<sup>3</sup>;  
<sup>1</sup>Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; <sup>2</sup>Res., Natl. Ctr. for Adaptive Neurotechnologies, Sauquoit, PA; <sup>3</sup>Natl. Ctr. for Adaptive Neurotechnologies, Natl. Ctr. for Adaptive Neurotechnologies, Delmar, NY; <sup>4</sup>NCAN, Stratton VA Med. Ctr., Natl. Ctr. for Adaptive Neurotechnologies, Stratton VA Med. Center, Albany, NY, Albany, NY

**Abstract:** Split-belt treadmill protocols are widely used to study the biomechanics of adaptations and motor learning. Most studies have been limited to one session; a few have included 2-6 sessions. We are studying the short-term adaptation and long-term impact of 24 training sessions in which the belts move at equal speed in opposite directions (bidirectional walking (BDW)). We previously reported that people adapt in one session to BDW. Stride length and joint ankles change. Here we report our first analyses of the effects of 24 BDW sessions on gait biomechanics, corticospinal excitability, and spinal reflexes. Six healthy people completed our

study. Each completed 24 BDW sessions (3/week). In each session, the person first walked for 2 min on a Bertec split-belt treadmill with both belts at 80% of their self-selected speed. This defined baseline gait for the session. They then walk for four 5-min training blocks separated by 1-min breaks with left-belt movement the same as baseline and right-belt movement at equal speed in the opposite direction. Lastly, they walked for 10 min with both belts in the same direction. Throughout the session, we recorded ground reaction forces; center-of-pressure; and EMG activity from tibialis anterior (TA), soleus, rectus femoris. and biceps femoris of both legs. In sessions 1, 7, and 12, 41 reflective markers and Qualysis motion capture recorded locomotor kinematics. Before session 1, after sessions 12 and 24, and 3 months later, we elicited in both legs: motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) in tibialis anterior (TA), soleus, rectus femoris. and biceps femoris; TA and soleus H-reflex recruitment curves; and sensory evoked potentials (SEPs) to vibrotactile and electrical stimulation to the foot sole and the tibial nerve, respectively. Preliminary results suggest that de-adaptation occurs progressively faster over sessions, as seen in stride length changes, accompanied by MEP changes. Further analyses will test our hypothesis that prolonged split-belt training will produce asymmetric changes in neurophysiological measures and in the EMG activity and kinematics of normal locomotion. In sum, we expect to find that the new BDW heksor produced by prolonged BDW training will modify the established heksor that produces normal locomotion. Locomotion will still be satisfactory, but locomotor EMG activity and kinematics will be different (DOI: 10.1113/JP283291)

**Disclosures:** **H. Mojtabavi:** A. Employment/Salary (full or part-time): national center for adaptive neurotechnologies, stratton va medical center. **R.L. Hardesty:** None. **D. Gupta:** None. **J. Wolpaw:** None.

## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.12/T15

**Topic:** F.06. Posture and Gait

**Support:** Bell Family Endowed Chair

**Title:** Characterizing stair ambulation biomechanics and the effects of dual tasking in Parkinson's disease

**Authors:** \***C. WALTZ**<sup>1</sup>, S. JONES<sup>1</sup>, E. ZIMMERMAN<sup>1</sup>, M. MILLER KOOP<sup>2</sup>, A. B. ROSENFELDT<sup>1</sup>, J. L. ALBERTS<sup>2</sup>;

<sup>1</sup>Cleveland Clin. Fndn., Cleveland, OH; <sup>2</sup>Cleveland Clin., Cleveland, OH

**Abstract: Background:** Stair ambulation is a demanding motor task that poses a considerable fall risk for people with Parkinson's disease (PwPD), particularly those with postural instability

and gait difficulty (PIGD) and those who experience unpredictable freezing of gait (FOG) episodes. Traditional functional mobility assessments often provide a single gross outcome, such as time, and do not evaluate the biomechanical nuances of real-world mobility. Although dual-task (DT) interference is well-characterized during level-ground walking, its effects on stair ambulation—an everyday task with elevated fall risk—are not well understood.

**Objective:** To characterize stair ambulation and functional mobility biomechanics in PwPD and to quantify the impact of dual tasking using the Stair Ambulation and Functional Evaluation of Gait (Safe-Gait) system, a custom-built staircase and walkway platform with embedded force plates and photoelectric timing gates.

**Methods:** Participants with Parkinson's disease performed three single-task (ST) and three dual-task (DT) trials on the Safe-Gait system. Kinetic data, captured via embedded force plates, were used to calculate step time, braking and propulsive impulses, and center of pressure (CoP) displacement and sway speed. Photoelectric timing gates segmented the task into five phases: stair ascent, walk-out, turn, walk-back, and stair ascent. Data from the timing gates were used to compute spatiotemporal outcomes.

**Results:** Compared to ST, DT conditions were associated with significantly longer step times ( $p < 0.001$ ), increased braking impulse ( $p < 0.01$ ), greater anteroposterior CoP range ( $p < 0.05$ ), and reduced mediolateral CoP speed ( $p < 0.01$ ). Under DT conditions, participants took approximately 22% longer to complete the task ( $p < 0.001$ ), with the largest differences in the stair ascent and walk-back phases.

**Conclusions:** The Safe-Gait system captured DT stair ambulation and functional mobility impairments in PwPD, reflected by slower and less stable gait patterns. These results underscore the effect of cognitive-motor interference on functional mobility and reinforce the value of instrumented stair assessments in informing clinical interventions and fall risk mitigation strategies.

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## **Poster**

### **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.13/T16

**Topic:** F.06. Posture and Gait

**Support:** The acknowledgment wording would include the grant number so it would be: "This research was funded in whole or in part by Aligning Science Across Parkinson's (ASAP-025185) through the Michael J. Fox Foundation for Parkinson's Research (MJFF).

**Title:** A motor observatory to track diverse mouse behavior

**Authors:** \*L. K. SCARIA<sup>1,3</sup>, L. KARASHCHUK<sup>1,3</sup>, H. F. M. RODRIGUES<sup>1</sup>, K. L. RUPP<sup>1</sup>, O. PATTON<sup>4</sup>, B. OUELLETTE<sup>1</sup>, C. GRASSO<sup>1</sup>, C. R. SCHMIDT<sup>1,3</sup>, A. M. VICENTE<sup>1,3</sup>, G. J. BERMAN<sup>4</sup>, S. J. SOBER<sup>4</sup>, R. M. COSTA<sup>2,3,1</sup>;

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**Abstract:** The nervous system has evolved to enable flexible movements in diverse situations. Understanding the structure of these varied movements is crucial to explaining the organization of the systems that produce these movements. Here, we introduce the Motor Observatory, an arena designed to capture diverse movements of mice (*Mus musculus*). The motor observatory arena has 12 cameras surrounding an open field with various clear playground objects like tunnels, wheels, climbing walls, (empty) treat feeders, and triangles. Using this arena, we collected a total of over 160 hours of behavior videos from 20 mice. We find that without any explicit reinforcement, mice explore and learn to perform various tasks such as climbing triangles and walls, grooming, jumping, rearing on cylinders, and turning the treat feeder. We use Anipose, a deep-learning-based 3D tracking framework, to track 47 mouse keypoints, capturing the movement of the body, limbs, and digits. We extended the Anipose optimization to support arbitrarily long videos and created a new web-based tool (Anivia) to support efficient 3D annotation. On average, we obtain an error of 2.6 mm relative to manual annotation (with inter-annotator error of 2.1mm). We devise a behavior labeling scheme to annotate this diverse data. Using these labels, we report initial analyses to understand the structure of these movements. We also show preliminary data of electromyography recordings from forelimb triceps muscles in the motor observatory. We hope to release the full dataset publicly, allowing other researchers to study diverse mouse movements.

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## **Poster**

**PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.14/U1

**Topic:** F.06. Posture and Gait

**Support:** NIH F32HD117548

**Title:** Neuromodulatory strategies targeting cortical and spinal neural pathways enhance paretic leg movement during walking in stroke

**Authors:** \*H. LIM<sup>1,2</sup>, S. YAN<sup>2</sup>, I. HAMEEDUDDIN<sup>3</sup>, W. Z. RYMER<sup>2</sup>, M. WU<sup>2,3</sup>;  
<sup>1</sup>Exercise and Sport Sci., Univ. of North Carolina, Chapel Hill, NC; <sup>2</sup>Shirley Ryan AbilityLab, Chicago, IL; <sup>3</sup>Univ. of Illinois, Chicago, IL

**Abstract: Background and Purpose:** Motor impairments in the paretic leg remain a major barrier to functional walking in individuals with stroke. This study investigated whether combining anodal transcranial direct current stimulation (a-tDCS) and spatiotemporal transcutaneous spinal cord stimulation (tSCS) improves motor control of the paretic leg more than tSCS alone during treadmill walking. **Methods:** In a sham-controlled, crossover design, fifteen individuals with chronic stroke participated in two sessions: a-tDCS+tSCS and tSCS alone during treadmill walking paired with targeted constraint force. The constraint force was applied to the swinging non-paretic leg to induce forced use of the paretic leg during treadmill walking. tSCS was delivered during the swing phase at 80 Hz, laterally to the paretic side at the L4 spinous process level, and during the stance phase at 30 Hz at the S1 level, both using a carrier frequency of 9.5 kHz. Spatiotemporal gait parameters, joint kinematics, muscle activity (EMG), spinal motoneuron activity, and propulsive force were measured pre-, during-, and post-treadmill walking. **Results:** The a-tDCS+tSCS led to greater increases in paretic step length and enhanced EMG activity of the paretic leg, specifically in the medial hamstring during stance and the tibialis anterior during swing, compared to tSCS alone. Spatiotemporal spinal map revealed greater spinal motoneuron activity at the L5 and S1 segments during stance, and at L4 and L5 during swing after a-tDCS+tSCS. Both conditions increased paretic stance time, joint angle of hip extension and ankle plantarflexion, EMG activity of medial gastrocnemius and soleus, and paretic propulsion; however, no significant between-condition differences were found. **Conclusion:** The combination of a-tDCS and spatiotemporal tSCS during treadmill walking paired with targeted constraint force may enhance phase-dependent activity of paretic leg muscles and spinal motoneurons, contributing to improved gait kinematics of the paretic leg. These findings suggest a synergistic effect of cortical and spinal stimulation, supporting the use of paired neuromodulation with task-specific training to enhance paretic leg movement during walking in individuals post-stroke.

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## **Poster**

**PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.15/U2

**Topic:** F.06. Posture and Gait

**Support:** NIH grant NS110550

**Title:** Effects of spinal transection and left-right speed differences between hindlimbs during split-belt treadmill locomotion on hindlimb muscle activity patterns

**Authors:** \*A. N. KLISHKO<sup>1</sup>, J. HARNIE<sup>2</sup>, I. A. RYBAK<sup>3</sup>, A. FRIGON<sup>4</sup>, B. I. PRILUTSKY<sup>5</sup>;  
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**Abstract:** We recently showed that major features of hindlimb muscle activity patterns during tied-belt treadmill locomotion are largely maintained after a low thoracic spinal transection across speeds in adult cats (Klishko et al., 2025). In this study, we investigated in the same nine adult cats of either sex the effects of a low thoracic spinal transection and left-right speed differences during split-belt treadmill locomotion on hindlimb EMG activity patterns, with the slow belt at 0.4 m/s and the fast belt at 0.5, 0.7 and 1.0 m/s. These experimental conditions introduce asymmetric sensory feedback and CPG inputs to left and right hindlimb muscles. EMG activities of 15 hindlimb muscles were recorded bilaterally during split-belt treadmill locomotion before and after spinal transection. Each hindlimb was investigated when stepping on the slow and fast belts. Major extensor muscles at the ankle (flexor digitorum longus, soleus, medial and lateral gastrocnemius, plantaris), knee (vastus lateralis) and hip (biceps femoris anterior, caudofemoralis, gluteus) in the slow- and fast-stepping hindlimbs demonstrated a single EMG burst during the stance phase in the intact and spinal-transected state. A one-joint hip flexor, the iliopsoas, and a two-joint hip flexor/knee extensor, the sartorius anterior, of the fast-stepping hindlimb demonstrated an additional EMG burst during the stance phase but only in the intact state and at fast belt speeds of 0.7 m/s and 1.0 m/s. The two-joint muscles, biceps femoris posterior and semitendinosus of the slow-stepping hindlimb also developed an additional EMG burst in the stance phase at the same fast belt speeds in the intact state. No additional EMG bursts compared to tied-belt treadmill locomotion were observed after spinal transection. The EMG magnitude of most extensors was higher during slow- than fast-stepping in both the intact and spinal-transected states although to a lesser degree in the latter. Both the spinal condition and the left-right speed difference affected EMG activity of all muscles. We concluded that the asymmetric CPG input and motion-dependent feedback differentially affect muscle activity in the intact and spinal-transected states.

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**Poster**

**PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.16/U3

**Topic:** F.06. Posture and Gait

**Support:** WVU Synergy Award

**Title:** Coordination, not load, drives the metabolic cost of walking with a powered knee prosthesis

**Authors:** \*S. TAHMID<sup>1</sup>, S. BAHIDASARIANTS<sup>2</sup>, S. HIME<sup>4</sup>, D. LANGLOIS<sup>5</sup>, N. R. GIRI<sup>3</sup>, R. A. GAUNT<sup>6</sup>, S. YAKOVENKO<sup>2</sup>;

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**Abstract:** Restoring leg function using artificial limbs is a problem of prosthetic design with competing engineering optimization decisions. The powered joints generate mechanical energy and may reduce the overall effort but are typically heavier than the non-powered alternatives. Another advantage of powered prosthetics is their participation in coordinated inter- and intra-limb actions. While there is currently no theoretical description of the optimal solution for the device's weight-power-coordination cost space, the metabolic cost can serve as an overall quantitative measure. Here, we tested the relative contribution of weight and coordination using a bypass adapter for a powered knee prosthetic leg. Healthy volunteers were instrumented with the bilateral surface EMGs and asked to walk on the force-sensitive treadmill belts at 0.5 and 0.75 m/s speeds while wearing a VO2 rate monitoring system. The data was collected in consecutive trials testing weighted and unweighted control, left leg loaded (same as the weight of a prosthetic with adapter), and left leg in a bypass adapter with the attached powered knee prosthetic limb. The metabolic cost of the additional weight was 6% when walking with the load; however, the cost increased to 59% when walking on the prosthetic. Additional unloading and stabilization were necessary to maintain stable locomotion. The staggered trial design revealed minimal effect of fatigue across trials. The significant speed-dependent increase in the metabolic cost of walking supports the idea that limited coordination drives the energy cost. Subjects could quickly adapt and compensate for the asymmetric load, but the prosthetic impeded this process in the short trials. Our preliminary study establishes the spectrum of function for improving the coordination within the prosthetic control system.

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## **Poster**

**PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.17/U4



**Topic:** F.06. Posture and Gait

**Support:** NIH Grant 1R21HD116115

**Title:** Increased error to knee movement during overground walking improves crouch gait in children with cerebral palsy

**Authors:** \*I. HAMEEDUDDIN<sup>1</sup>, H. LIM<sup>2</sup>, S. YAN<sup>3</sup>, M. WU<sup>4</sup>, W. Z. RYMER<sup>2</sup>;

<sup>1</sup>Univ. of Illinois at Chicago, Bolingbrook, IL; <sup>2</sup>Shirley Ryan AbilityLab, Chicago, IL; <sup>3</sup>Shirley Ryan AbilityLab, Northwestern Univ., Chicago, IL; <sup>4</sup>Legs and Walking lab, Shirley Ryan Abilitylab- Chicago, CHICAGO, IL

**Abstract:** A common gait disorder caused by cerebral palsy (CP) is crouch gait, the hyperflexion of hip, knee, and ankle joints; this leads to less efficient gait and overstrengthening of muscles. Current treatments do not effectively target key deficits; as such, a deeper understanding of motor learning mechanisms in crouch gait is needed. The purpose of this study is to determine whether increasing errors with targeted resistance will be more effective than decreasing errors with assistance to improve crouch gait. We hypothesized that increasing errors by applying resistance during mid-swing phase to the knee will facilitate motor learning of improved gait with less hyperflexion. Eleven participants (age 10-15, 4 girls, GMFCS I-III) with crouch gait participated in a 1-visit study to walk overground in two conditions: increasing error (Resist) or decreasing error (Assist) to the knee movement during swing phase of gait. Each condition consisted of an 8-minute walk: 1 minute no force (baseline), 5 minutes force applied (adaptation), and 2 minutes no force (post-adaptation). After a short break, the participant walked another 3 minutes with the force (re-adaptation). Before, after, and 10-minute after each condition, the participants completed 6 trials of walking on the GaitRite and a 1-minute walk on the split-belt treadmill. During each condition, Assist or Resist force is applied to the knee joint for 250ms at mid-swing phase; the magnitude of force was 4-8% of body weight. The force was applied via a custom wearable robotic system with a backpack portion housing the motor attached to a knee brace via a pulley system to actuate the knee to either resist knee extension or assist knee extension during swing. Participants adapted to the error-augmented force and showed aftereffects with changes in peak knee flexion and peak hip extension during the post-adapt period. Specifically, they demonstrated significant increase in peak hip extension ( $\Delta 4.17^\circ$ ,  $p < 0.05$ ) and a decreased knee flexion pattern in the Resist condition, but showed a significant increase in knee flexion ( $\Delta 3.5^\circ$ ,  $p < 0.05$ ) with a pattern of decreased hip extension in the Assist condition. They also showed significant decrease in EMG activity in both conditions for the rectus femoris and hip adductors, and significant decreases in the hamstring and vastus medialis with the Assist condition ( $p < 0.05$ ). These results suggest that increasing errors via resistive force, as opposed to decreasing error via assistive force, to the knee movement during swing phase may be more effective in improving crouch gait. Results from this study may be used to develop new, more effective interventions to improve crouch gait in children with CP.

**Disclosures:** I. Hameeduddin: None. H. Lim: None. S. Yan: None. M. Wu: None. W.Z. Rymer: None.

**Poster**

## **PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.18/U5

**Topic:** F.06. Posture and Gait

**Support:** the National Multiple Sclerosis Society in the USA (project RG-2206-39688)

**Title:** Classifying the center of pressure trajectory under colored, noisy galvanic vestibular stimulations using machine learning techniques

**Authors:** \*N. RAHIMI<sup>1</sup>, V. HATZITAKI<sup>2</sup>, A. KAMANKESH<sup>1</sup>, A. GAVRIILIDOU<sup>3</sup>, R. M. ENOKA<sup>1</sup>;

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**Abstract:** We compared the accuracy with which a machine-learning algorithm could distinguish among center-of-pressure (CoP) trajectories during upright standing when noisy galvanic vestibular stimulation (nGVS) was applied at intensities relative to perceptual threshold. Three machine learning models—decision tree, random forest, and K-nearest neighbors (KNN)—were evaluated using CoP data collected from 40 young, healthy adults standing on a firm surface with feet together and eyes closed.

A total of 7 time-domain features and 84 bandwidths in each axis in the time-frequency domain, with the latter derived with continuous wavelet transform (CWT) for each of the x- and y-axes, were extracted from the CoP trajectories. The top three most important time-domain features—Time, CoPx (side-to-side), and CoPy (forward-backward)—were identified using permutation feature importance. The two most relevant time-frequency features, located in the 0.11-0.16 Hz band for both axes, were selected using correlation-based feature selection. Models were developed to determine classification accuracy in four conditions derived from combinations of stimulus intensity (% perceptual threshold), type of superimposed noise (pink or white), and the responsiveness of participants to the perturbation.

Among all models, the KNN algorithm achieved  $\geq 96\%$  classification accuracy in all four conditions, which indicates that the CoP trajectories were unique at each level within all the conditions. Although the two time-frequency features (CTWx, CWTy) outperformed the two time-domain features (CoPx, CoPy), similar accuracy was achieved using the top three time-domain features (Time, CoPx, and CoPy) and the top two time-frequency features (CTWx, CWTy). Notably, the model was able to discriminate the features extracted from CoP trajectories for participants who either did or did not exhibit a stochastic-resonance effect in response to nGVS. SHapley Additive exPlanations (SHAP) analysis further revealed that the contribution of the five extracted features in classifying these two groups of participants was greater during the White-noise condition. Overall, these findings indicate that nGVS induces condition-specific modulation of CoP trajectories, features extracted from CoP trajectories were distinct, and that machine learning techniques can effectively capture and classify these effects.

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**Poster**

**PSTR227: Exploring Posture and Gait: Insights Into Kinematics, Muscle Activity, Exercise, Fatigue, and Biomechanics**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR227.19/U6

**Topic:** F.06. Posture and Gait

**Support:** Lundbeck Foundation Postdoctoral Fellowship

**Title:** Spinal Neural Dynamics Remap Across Gaits Without Circuit Switching

**Authors:** \*O. REFY<sup>1</sup>, O. SATO<sup>2</sup>, K. SOBRIEL<sup>1</sup>, M. CARBO TANO<sup>1</sup>, R. W. BERG<sup>1</sup>;  
<sup>1</sup>Neurosci. Dept., Univ. of Copenhagen, Copenhagen, Denmark; <sup>2</sup>Harvard Univ., Boston, MA

**Abstract:** A longstanding question in motor neuroscience is whether different locomotor gaits are controlled by distinct spinal modules or by a single circuit operating in multiple dynamical modes [1]. To address this, we recorded from hundreds of single units in the lumbar spinal cord of freely moving rats (n=2) using implanted high-density probes (Neuropixels) during naturalistic gaits, including walking, trotting and galloping. Step-aligned neural activity was analyzed using dimensionality reduction, temporal tuning, and neuron participation metrics. We found that spinal population activity occupied distinct low-dimensional manifolds for each gait, with transitions marked by abrupt remapping of neural trajectories. However, the underlying neural circuitry was largely preserved: on average, ~85% of neurons participated across all gaits, with gait-dependent shifts in temporal activity profiles rather than recruitment of different units. These results suggest that multiple gaits are generated by reconfiguration of dynamics within a shared spinal network, rather than by recruitment of discrete modular circuits. [1] Kiehn, O. Decoding the organization of spinal circuits that control locomotion. *Nat Rev Neurosci* **17**, 224-238 (2016). <https://doi.org/10.1038/nrn.2016.9>

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**Poster**

**PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.01/U7

**Topic:** F.06. Posture and Gait

**Support:** NASA West Virginia Space Grant Consortium, Grant 80NSSC25M7079  
NSF CRCNS 2113028

**Title:** Dynamical sensory neuron force measurements improve performance of Carausius morosus robot to perturbations

**Authors:** \*I. M. KUDYBA<sup>1</sup>, S. N. ZILL<sup>2</sup>, N. S. SZCZECINSKI<sup>1</sup>;

<sup>1</sup>Mechanical, Materials, and Aerospace Engin., West Virginia Univ., Morgantown, WV;

<sup>2</sup>Biomed. Sciences/Anatomy, J.C. Edwards Sch. Med., Huntington, WV

**Abstract:** To enable robust and adaptive standing and walking, animals have mechanosensors that measure resisted forces and enhance motor control. Mechanoreceptors in insects, campaniform sensilla (CS), are shown to dynamically encode external forces, responding with higher frequencies when force increases and silencing when force decreases. The dynamic response of CS lets them act as a phase lead compensators, a type of high pass filter, for motor neuron activation. We hypothesize that the CS dynamic response allows insects to predict and quickly respond to changing environmental forces. How does the dynamic response of force sensors impact the ability of animals to control locomotion? In this study, we perturbed a robotic stick insect and measured resulting strains at locations of CS fields. We incorporated force feedback by applying different phase lead compensators modeled after stick insect CS recordings, a controller based on the viscoelasticity of the leg, and a control in which no force feedback was incorporated. The controllers' success was measured by comparing the root mean squared error of the joint's positions. This data is useful to understand how intricate dynamics of sensory neurons are beneficial to motor control in walking and standing. Additionally, by applying biological inspired controllers in robots, this work may improve the design of walking robots enabling them to robustly adapt to environmental changes.

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## **Poster**

**PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.02/U8

**Topic:** F.06. Posture and Gait

**Title:** Age-dependent modulation of low-frequency postural sway oscillations reveals sensory reweighting across the lifespan.

**Authors:** \*V. ROBLES-CERDAS<sup>1</sup>, N. M. A. ALSALMIE<sup>2</sup>, M. MEYER VEGA<sup>2</sup>, N. SHAH<sup>2</sup>,  
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<sup>1</sup>Sch. of Kinesiology, <sup>2</sup>Auburn Univ., Auburn, AL

**Abstract:** Postural sway is regulated through the integration of three primary sensory systems: vision, proprioception (somatosensory), and the vestibular system. The Modified Clinical Test of Sensory Interaction in Balance (mCTSIB) is a widely used tool to assess an individual's reliance on each of these systems. By presenting varied sensory conditions, the mCTSIB not only identifies sensory dependence but also serves as a valuable platform for balance training and rehabilitation. Emerging evidence suggests that low-frequency oscillations in postural sway (0-4 Hz) encode information about the relative contributions of each sensory system to postural control. We aimed to examine how visual, proprioceptive, and vestibular inputs interact to maintain balance across the lifespan. Specifically, we sought to understand how sensory integration patterns evolve with age, reflected in the frequency characteristics of postural sway during sensory-challenged conditions. We tested four hundred and forty-six healthy individuals (175 males and 271 females) between ages of 5 and 83 years ( $31 \pm 18$  years). Each subject was tested under four conditions on a force plate: 1) Quiet standing with eyes open - on a firm surface (standard); 2) Quiet standing with eyes closed (somatosensory); 3) Quiet standing with eyes open on a foam cushion (visual), and 4) Quiet standing with eyes closed on a foam cushion (vestibular). We find that Center of Pressure ( $F = 13.35$ ,  $p < .001$ ), anterior-posterior ( $F = 14.093$ ,  $p < .001$ ), mediolateral ( $F = 8.608$ ,  $p < .001$ ) sway path lengths were significantly different across conditions (standard < visual < somatosensory < vestibular) and age-groups ( $F = 22.908$ ,  $p < .001$ ). 0-4 Hz oscillations similarly scaled from standard < visual < somatosensory < vestibular conditions and were significantly different across test conditions ( $F = 3.238$ ,  $p < .001$ ) and age-groups ( $F = 4.345$ ,  $p < .001$ ). Our findings underscore the value of the mCTSIB paired force plate analysis, as a powerful tool for quantifying the dynamic interplay of visual, vestibular, and proprioceptive inputs in postural control. This approach not only reveals age-related shifts in sensory dependence but also offers a sensitive, objective method for assessing balance integrity across the lifespan - supporting both clinical decision-making and targeted intervention strategies.

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## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.03/U9

**Topic:** F.06. Posture and Gait

**Support:** NSF GRFP  
NSF 23-511 Biology Integration Institutes

**Title:** Exoskeleton Influence on Human Joint Level Force Responsiveness and Control

**Authors:** \*A. ALSHAREEF<sup>1</sup>, G. S. SAWICKI<sup>2</sup>;  
<sup>2</sup>Mechanical Engin., <sup>1</sup>Georgia Inst. of Technol., Atlanta, GA

**Abstract:** Exoskeletons have advanced significantly in the past few decades. Although exoskeletons have been developed to achieve certain energetic or stability outcome metrics, the way they interact with our governing sensorimotor control system may have unintended impacts on overall agility and stability. Recent work has begun to quantify human force responsiveness (Kudzia et al, 2022). Here we measure human force responsiveness and control with and without exoskeletal assistance in isolated joint, torque matching tasks. Three young adults wearing an ankle exoskeleton were placed in a dynamometer to measure ankle torque output during isometric contractions. Participants were given an auditory metronome, a visual target line on a screen of the torque target to reach, and visual feedback of their real-time torque. Six randomized trial conditions were conducted, with 3 torque targets at 20%, 40%, and 60% of maximum contraction with and without exoskeleton assistance, and 10 steps within each trial. The set of trials was repeated three times to investigate potential motor adaptation. The step responses were quantified using classical controls metrics including bandwidth, overshoot, steady-state error, and steady-state variability. Higher bandwidth indicates higher responsiveness, and a lower steady-state error and steady-state variability indicates greater accuracy. Increased torque targets correlated with lower responsiveness and lower accuracy for the system. In the first repetition, both the NT condition and the PMC conditions had a similar bandwidth across conditions, however subsequently the bandwidth of the PMC condition increased for the 40% and 60% targets ( $0.2975 \pm 0.6528$  Hz and  $0.227 \pm 0.271$  Hz), indicating potential adaptation to the exoskeleton assistance and improved responsiveness as opposed to the NT condition. Steady-state variability increased for the NT condition across torque targets between the first and second repetition, while remaining consistent in the PMC condition across repetitions. The improved performance of PMC in the second repetition suggests a potential benefit of exoskeleton assistance to the inherent sensorimotor control system's accuracy and responsiveness after adaptation and sensory reweighting. Investigating the effects of exoskeleton assistance on human force responsiveness will provide insights into the human sensorimotor control loop during physiologically relevant excursions. Modeling the human neuromuscular system as a feedback control system and incorporating external exoskeletal influences can offer crucial insights into the effects of exoskeletons the sensorimotor feedback.

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## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.04/U10

**Topic:** F.06. Posture and Gait

**Support:** NIH Grant HD032571

**Title:** Stretch reflex removal from anterior thigh muscles alters hindlimb muscle activity and interlimb coordination during cat locomotion: implications for balance control

**Authors:** \*C. E. HANSON<sup>1,2</sup>, R. MEHTA<sup>2</sup>, A. N. KLISHKO<sup>2</sup>, S. AMIN<sup>2</sup>, R. J. GREGOR<sup>2</sup>, A. FRIGON<sup>3</sup>, T. AKAY<sup>4</sup>, B. I. PRILUTSKY<sup>2</sup>;

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**Abstract:** Somatosensory feedback during quadrupedal locomotion is integrated within the spinal locomotor network of each limb via commissural and propriospinal pathways to ensure an appropriate number of limbs are contacting the ground to maintain balance (Frigon et al., 2021). It was suggested that length-dependent feedback from proximal limb muscles regulates stance-swing and swing-stance transitions (Pearson, 2004). Compromising this feedback might also affect balance control. The goal of this study was to examine the effects of removing a component of length-dependent feedback (stretch reflex) from the vasti (VA, knee extensor), rectus femoris (RF, hip flexor/knee extensor) and sartorius (SRT, hip flexor/knee flexor/knee extensor) using self-reinnervation (Cope et al., 1994; Lyle et al., 2016) on hindlimb electromyographic (EMG) activity, interlimb coordination and lateral balance. We hypothesized that compromising length feedback from hip flexors RF and SRT would impair balance control and lead to locomotor adaptations aimed at improving stability (e.g., increasing the step width, decreasing the height of the center of mass (COM), increasing margins of stability). In addition, we hypothesized that disrupting length-dependent feedback from the VA and RF would differentially affect EMG activity of these muscles because the activity of the latter was suggested to depend more on motion-dependent sensory feedback (Markin et al., 2012). We recorded 3D full-body mechanics and hindlimb EMG activity during overground walking of 7 adult female cats before and after self-reinnervation of the right VA, RF and SRT muscles by transecting the corresponding nerve branches and immediately reconnecting them together. Muscle self-reinnervation was confirmed by recovery of EMG signal from the VA and RF 4-6 months after surgery. After completing data collection, the absence of stretch reflex in the VA and RF was verified in terminal experiments (Lyle et al., 2016). We found that removing the stretch reflex from the right VA, RF and SRT decreased walking speed, increased hindlimb step width, and increased the ipsilateral margin of lateral dynamic stability. The mean COM position in the cycle was lower and shifted rostrally, while the contralateral hindlimb and forelimb were more extended and flexed, respectively. We also found that removing the stretch reflex from VA and RF significantly affected the EMG activity pattern and burst duration of RF, but had minimal impact on the VA and other hindlimb muscles. The results are consistent with the role of length-dependent feedback from anterior thigh muscles in the control of interlimb coordination and balance during locomotion.

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**Poster**

**PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.05/U11

**Topic:** F.06. Posture and Gait

**Support:** JSPS KAKENHI 23K27943  
JSPS KAKENHI JP22H03442

**Title:** Transcutaneous spinal cord stimulation phase-dependently modulates spinal reciprocal inhibition induced by pedaling in healthy individuals

**Authors:** \*K. TAKANO<sup>1,2,3</sup>, T. YAMAGUCHI<sup>4,5</sup>, K. KIKUMA<sup>2</sup>, K. OKUYAMA<sup>2</sup>, N. KATAGIRI<sup>1,2,3</sup>, T. SATO<sup>1,2</sup>, S. TANABE<sup>6</sup>, K. KONDO<sup>2</sup>, T. FUJIWARA<sup>1,5</sup>;

<sup>1</sup>Juntendo Univ. Grad. Sch. of Med., Bunkyo, Japan; <sup>2</sup>Tokyo Bay Rehabil. Hosp., Narashino, Japan; <sup>3</sup>JSPS, Chiyoda, Japan; <sup>4</sup>Kyoto Univ. Grad. school of Med., Kyoto, Japan; <sup>5</sup>Juntendo Univ. Fac. of Hlth. Sci., Bunkyo, Japan; <sup>6</sup>Sch. of Hlth. Science, Fujita Hlth. Univ., Toyoake, Japan

**Abstract:** Reciprocal inhibition (RI) plays an essential role in the smooth movement. RI is often impaired in patients with stroke, and impaired RI contributes to abnormal muscle co-activation during locomotion. Pedaling is a rhythmic movement that can increase RI in healthy individuals but not in patients with severe stroke. Transcutaneous spinal cord stimulation (tSCS) stimulates spinal neural circuits by targeting afferent fibers. Pedaling with simultaneous tSCS may modulate the plasticity of the spinal neural circuit, altering neural activity based on movement and muscle engagement. This study investigated the RI changes after pedaling combined with tSCS and determined the phase of pedaling in which tSCS should be applied for optimal RI modulation in healthy individuals. Eleven subjects underwent three interventions on different days: pedaling combined with tSCS during the early phase of lower extension (when the moment of maximum left hip flexion during pedaling is set as 0°, the range from 0° to 90°; phase 1), pedaling combined with tSCS during the late phase of lower flexion (the range from 270° to 360°; phase 4) of the pedaling cycle, and pedaling combined with sham tSCS. Active pedaling was performed at a comfortable speed for 7 minutes, while maintaining a constant pedal resistance of 5 Nm throughout the pedal cycle, regardless of the pedal speed. For tSCS, a monophasic 100 Hz current (1 ms pulse width) was applied at the stimulation intensity of the motor thresholds of the trunk muscles for the activation of afferent fibers. The cathodal electrode was placed on the skin over the Th11-Th12 spinous processes, and an anodal electrode was placed on the trunk above the umbilicus. At the assessment of RI, disynaptic reciprocal Ia inhibition from the tibialis anterior to the soleus muscle was assessed before, immediately after, 15 min, and 30 min after the intervention. A two-way repeated measures analysis of variance of the factors of the interventions and time, and t-tests with Bonferroni adjustments for multiple comparisons were performed. In the results, RI increased immediately after phase 4 ( $P = 0.02$ ) and pedaling combined with sham tSCS ( $P = 0.01$ ), whereas no changes were observed after phase 1 ( $P > 0.05$ ). These results demonstrate that tSCS modulates RI changes induced by pedaling in a stimulus phase-dependent manner in healthy individuals. Further studies are needed to evaluate the therapeutic effects of this pedaling combined with tSCS in patients with stroke for its clinical application.



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**Poster**

**PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.06/U12

**Topic:** F.06. Posture and Gait

**Support:** Swiss National Science Foundation (32003B\_208110)

**Title:** Probing the role of the reticulospinal system in locomotor coordination

**Authors:** \*N. S. HOLLIGER<sup>1,2</sup>, V. DIETZ<sup>1</sup>, M. GEISSMANN<sup>3</sup>, L. FILLI<sup>1,3</sup>;

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**Abstract:** Locomotor coordination, including interlimb coupling, is essential to maintaining dynamic stability and regulating effective walking. While locomotor coordination is assumed to be mediated by different neural structures, their specific roles are not fully understood. In a previous study, we found evidence that the reticulospinal (RS) system is involved in the neural coordination of bilateral hand movements. The present study aims to investigate the potential involvement of the RS system in locomotor coordination. Nineteen healthy participants walked on a treadmill integrated into the virtual reality environment of the GRAIL system. To investigate interlimb coordination via interlimb coupling, unilateral electrical stimuli (ES) were applied to the right tibial nerve. Additionally, loud acoustic stimuli (LAS) were delivered to probe the contribution of RS drive to the neural coupling of leg movements during locomotion. A motion capture system enabled the real-time application of ES and LAS during either the swing or double support phase of the right leg. Electromyographic (EMG) activity was assessed from the tibialis anterior (TA) and medial gastrocnemius (GM) muscles. Four assessment blocks were performed with each block consisting of 12 LAS and 12 ES trials. ES applied during the swing phase elicited neural coupling responses in the contralateral GM and TA muscles, with more pronounced responses observed in the GM. A similar response pattern was observed following LAS released during the swing phase: LAS-evoked EMG responses resembled the ES-induced responses in both amplitude and configuration but occurred earlier. During the double support phase, both ES- and LAS-induced EMG responses were markedly reduced, suggesting a phasic modulation of descending motor drive throughout the gait cycle. The strong similarity of LAS- and ES-evoked responses supports the notion that these coupling reflexes are mediated by the RS system. These findings provide indirect evidence that the RS system contributes to interlimb coordination during locomotion.

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**Poster**

**PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.07/U13

**Topic:** F.06. Posture and Gait

**Title:** Auditory effect on the soleus H-reflex in young and elderly adults during two postural conditions.

**Authors:** \*D. M. KOCEJA<sup>1</sup>, N. RAJAEIAN<sup>2</sup>, P. HASSANNIA<sup>2</sup>, K. KITANO<sup>2</sup>;  
<sup>2</sup>Kinesiology, <sup>1</sup>Indiana Univ., Bloomington, IN

**Abstract:** There have been numerous studies addressing the relationship between human postural control and the modulation of spinal networks. It is known that auditory inputs have facilitatory effects on the soleus H-reflex (Startle Effect) proposed to originate from the reticulospinal tract. Both the corticospinal and reticulospinal tracts are instrumental during postural control, impinging either directly onto motoneurons or interneurons. The purpose of the current study was to investigate the effects of postural difficulty on auditory facilitation of the soleus H-reflex in young and elderly subjects. Ten young (age < 30 years) and four elderly (age > 80 yrs) subjects participated in the study. Surface EMG was recorded from the soleus muscle. The H-reflex was evoked by stimulating the tibial nerve at the popliteal fossa. The auditory sound was a 700 Hz square wave with a duration of 30 msec and was delivered through a headset with the sound level set at 75 dB. Each subject was tested under two conditions with eyes open: standing on floor (low difficulty); and standing on a foam exercise pad (higher difficulty). For each condition, 20 H-reflex trials were administered in a random order: 10 were H-reflex only trials (unconditioned) and 10 were H-reflex trials which were elicited 60 ms after the initiation of the auditory stimulus. The peak-to-peak amplitude of the H-reflex for each condition was averaged and a gain value (Auditory H-reflex/Unconditioned H-reflex) was calculated. For the floor condition (low difficulty) there was a significant increase caused by the auditory stimulus for the young (mean gain = 135%,  $p = 0.002$ ) but not the elderly (mean gain = 97%). Both groups showed an attenuation for the auditory effect when standing on the foam pad, again with the young demonstrating a significant but smaller facilitation (mean gain = 117%,  $p = 0.05$ ) and the elderly demonstrating more inhibition (mean gain = 87%). In both conditions there was a significant difference between young and elderly. A reduction in the auditory facilitation observed in a more challenging environment, during which more accurate postural control is required, suggests that the facilitatory effect on the soleus H-reflex is environment-dependent, and this effect appears to diminish with age.

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**Poster**

## **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.08/U14

**Topic:** F.06. Posture and Gait

**Support:** NIH R21  
NSF CRCNS US-Japan  
The Wu Tsai Human Performance Alliance at Stanford University  
Fellowships from USC Viterbi School of Engineering

**Title:** Influence of skeletofusimotor vs. fusimotor systems on the neuromechanics of quadruped locomotion

**Authors:** \*G. NIYO<sup>1</sup>, F. J. VALERO-CUEVAS<sup>2</sup>;

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**Abstract:** Vertebrates can adapt their locomotion to surfaces with a range of mechanical properties by modulating leg impedance (often over-simplified in the literature as ‘stiffness’) [1-5]. This ability has been ascribed to the physiological ability to modulate sensory-driven spinal reflexes including those from spindle afferents [6-9]. Such modulation can happen at the level of the reflex gains, which can be achieved by several mechanisms—which are yet to be fully understood. These include control of the intrafusal fibers (via  $\beta$ - and  $\gamma$ -MN activation) that adjust the sensitivity of the muscle spindle mechanoreceptors to overall muscle fiber stretch; as well as via presynaptic gain modulation at the level of the  $\alpha$ -MN pool [10]. There are, however, critical neuro-architectural differences between the  $\beta$ -MNs (mostly in amphibian and reptiles, but also present in mammals) and  $\alpha$ -,  $\gamma$ -MNs (dominant in mammals) [11, 12].  $\beta$ -MNs co-innervate both muscle spindle intrafusal fibers and extrafusal fibers, constituting a skeleto-fusimotor system. In contrast,  $\gamma$ -MNs and  $\alpha$ -MNs, are thought to provide selective individual control of spindle intrafusal fibers and extrafusal fibers, respectively, enabling the decoupling of force production from spindle sensitivity [10, 12]. In this study, we employ neuromechanical simulations of a tendon-driven quadruped to compare the mechanical properties of  $\beta$ -driven skeleto-fusimotor versus  $\alpha$ -, and  $\gamma$ -driven architectures during locomotion on terrains of different mechanical properties. This work provides a new comparative framework for evaluating the evolutionary and functional implications of motoneuron specialization. References:[1]. Ferris DP, Farley CT. J Appl Physiol 82.1 (1997), pp. 15-22.[2]. Farley CT, Ferris DP. Exerc Sport Sci Rev 26.1 (1998), pp. 253-286.[3]. Ferris DP, Liang K, Farley CT. J Biomech 32.8 (1999), pp. 787-794.[4]. Full RJ, Farley CT, Winters JM. In: Biomech Neural Control Posture Move, Springer (2000), pp. 192-205.[5]. Dickinson MH et al. Science 288.5463 (2000), pp. 100-106.[6]. Houk JC. Annu Rev Physiol 41.1 (1979), pp. 99-114.[7]. McMahon TA. Muscles, Reflexes, and Locomotion. Princeton Univ Press, 1984.[8]. Brown IE, Loeb GE. In: Biomech Neural Control Posture Move, Springer (2000), pp. 148-163.[9]. Niyo G et al. PNAS 121.34 (2024), e2321659121.[10]. Pierrot-Deseilligny E, Burke D. The Circuitry of the Human Spinal Cord. Cambridge Univ Press, 2005.[11]. Llinás R, Precht W. Frog Neurobiology. Springer, 2012.[12]. Manuel M, Zytnicki D. J Integr Neurosci 10.3 (2011), pp. 243-276.

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**Poster**

**PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.09/U15

**Topic:** F.06. Posture and Gait

**Support:** NIH Grant HD084188

**Title:** Transtibial prosthesis actuated by residual muscles and generating motion-dependent proprioceptive feedback

**Authors:** B. FARRELL<sup>1</sup>, P. NARDELLI<sup>2</sup>, Y.-H. CHANG<sup>2</sup>, A. N. KLISHKO<sup>2</sup>, T. C. COPE<sup>3</sup>,  
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**Abstract:** Many amputees are still dissatisfied with available limb prostheses and often reject body-powered or electric arm prostheses and prefer to use non-prehensile prostheses as cosmetic devices (Biddiss, Chau, 2007). Only recently researchers have started exploring possibilities of controlling limb prostheses by direct signals from the nervous system and providing natural motion-dependent feedback. We proposed a novel limb prosthetic design, in which residual muscles are directly attached to a prosthetic device through alloplastic tendons and bone implant (Farrell et al., 2017). This design can potentially allow the user to actuate the prosthesis by contracting the residual muscles and to perceive prosthetic motion and loading via proprioceptors in the residual muscles. Here, we examined in the rat model if (1) the proposed design would allow actuation of a prosthetic foot by the residual ankle flexors and extensors during locomotion and (2) motion of this transtibial prosthesis would generate activity of proprioceptive afferents in the residual muscles. A bone-anchored transtibial prosthesis consisted of (i) the stainless-steel implant in tibia marrow canal, (ii) artificial tendons (nitinol monofilaments) attached to the residual tibialis anterior and soleus/gastrocnemius muscles wrapped by propylene mesh, and (iii) the prosthetic foot and ankle. The prosthesis was implanted in 5 female Lewis rats. Before and 5-14 days after surgery, we used high speed biplane X-ray video (Kirkpatrick et al., 2022) to record kinematics of rat treadmill locomotion. After locomotion experiments, 3 out of 5 implanted rats underwent terminal experiments in which responses of proprioceptive afferents of the residual gastrocnemius to imposed prosthesis movements (ramp-hold-release, triangle and sine waves, 100Hz vibration) and muscle electrical stimulations were recorded in the dorsal roots (Rotterman et al., 2023). Although major kinematic characteristics of prosthetic locomotion (stride, stance and swing durations; hip and knee angle changes in stance) were not different from intact locomotion, the ankle extension in stance was ~3 times smaller than before surgery, but not zero ( $9.1 \pm 4.7^\circ$ ,  $p < 0.05$ ). Imparting external prosthetic ankle perturbations in anesthetized rats revealed responses of spindle group Ia and II and Golgi tendon organ group Ib

afferents that were qualitatively similar to those of the control animals. We concluded that it is possible in principle to operate the limb prosthesis by the actions of residual muscles which also provide natural motion-dependent proprioceptive feedback.

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## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.10/U16

**Topic:** F.06. Posture and Gait

**Title:** Effect of sensory feedback with treadmill training on spatiotemporal gait parameters and function in individuals with neurological disorders: A systematic review and meta-analysis

**Authors:** \*K.-H. SU, Y.-N. LIU, W.-T. WANG, Y.-F. SHIH, H.-J. LUO, H.-T. SHIH;  
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**Abstract:** Treadmill training can effectively improve gait in limited treatment spaces and is widely used in clinics. To further enhance its efficacy, previous studies have combined sensory feedback with treadmill training for treating people with neurological diseases, but have shown heterogeneous results. Therefore, we aimed to conduct a meta-analysis to quantitatively evaluate the effect of treadmill training combined with sensory feedback. Additionally, we examined whether the effect was impacted by participants' diagnosis or the types of sensory feedback. The databases we searched included PubMed, PEDro, MEDLINE, CINAHL, ScienceDirect, Web of Science, Embase, and Scopus. To be encompassed in the analysis, studies must be intervention trials with a control group, have an experimental group receiving concurrent sensory feedback and treadmill training, recruit adults with neurological disorders, and measure gait parameters and function. After title, abstract, and full-text screening, a total of 21 studies remained in our systematic review, and 20 in the meta-analysis (Stroke 15, Parkinson's disease 4, Multiple sclerosis 1). Outcomes spanned from gait speed, spatiotemporal parameters, to function (i.e., Berg Balance Scale, Timed Up and Go, and walking distance). We further conducted subgroup analyses by populations and types of sensory feedback. All outcomes were analyzed using change scores and presented with standardized mean difference (SMD). Results showed that the combination of treadmill training and sensory feedback significantly outperformed interventions without sensory feedback on gait speed ( $n = 19$ ;  $SMD [95\% CI] = 0.768 [0.462, 1.075]$ ,  $p < .001$ ), and the efficacy was consistent in people with stroke ( $n = 14$ ;  $0.687 [0.395, 0.978]$ ,  $p < .001$ ) and Parkinson's disease ( $n = 4$ ;  $1.237 [0.178, 2.296]$ ,  $p = .022$ ). Similar superior effects were found in gait spatiotemporal parameters ( $SMD \text{ range} = -0.477 \text{ to } 1.237$ ,  $p < .001 \text{ to } p = 0.15$ ), walking distance ( $n = 7$ ;  $0.641 [0.204, 1.077]$ ,  $p = .004$ ), Berg Balance Scale ( $n = 4$ ;  $0.743 [0.337, 1.149]$ ,  $p < .001$ ), and Timed Up and Go ( $n = 9$ ;  $-0.421 [-0.669, -0.173]$ ,  $p = .001$ ). Visual, auditory, and combined feedback all significantly improved participants' gait speed

compared to the control group, yielding moderate effect sizes (SMD range = 0.495 to 0.772). In conclusion, treadmill training with sensory feedback induced significantly more improvement on various aspects of gait and function than those without in individuals with neurologic diseases. When utilizing a treadmill for gait training, physical therapists may consider incorporating sensory feedback, regardless of the type, to maximize the training effect.

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## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.11/V1

**Topic:** F.06. Posture and Gait

**Title:** Gait kinematics are altered when reach and grasp complexity are increased

**Authors:** \*C. S. LAYNE<sup>1</sup>, A. N. AKINRINADE<sup>2</sup>, E. O. HERNANDEZ<sup>4</sup>, N. DE LA CRUZ GARCÍA<sup>4</sup>, C. A. JOHNSTON<sup>2</sup>, D. MARTINEZ DIAZ<sup>3</sup>;

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**Abstract:** Introduction: The results of early work combining gait with reach and grasping tasks were often interpreted as supporting a ‘posture first’ approach to movement control. This suggested that postural stability was prioritized over the reaching task. Subsequent experiments utilizing more complex grasping tasks indicated that posture first control may not be universal. Emotional factors such as anxiety can also modify gait. Purpose: To assess selected gait metrics associated with two levels of complexity of a reaching and grasping task while walking.

Methods: Subjects: 20 right-handed and footed ( $\bar{X}$  age - 22.5, SD - 4.5, 10 females). The task was to walk at a self-selected speed from a fixed starting position and pick up a cowbell placed on a table and continue walking. In one condition the instructions were to prevent the cowbell from ringing (R condition). In the second condition, the bell was mechanically prevented from ringing (NR condition). No instructions were provided about which foot to begin walking with.

Subjects were required to always pick the bell up by the handle, ensuring the grip aperture was the same in each condition. Bilateral sagittal plane kinematics of the hip, knee, shoulder and elbow were obtained using a markerless motion capture system. Measures: Each trial was visually inspected to obtain: 1) walking initiation foot, 2) foot on ground at moment of bell contact, 3) stride times associated with footfall patterns, 4) joint range of motions (ROM) and 5) peak joint velocities. Besides foot initiation, this report only concerns data obtained during the stride at which the bell was grasped. Results: Independent of condition, significantly more strides were initiated with the ipsilateral (i.e. right foot) with no difference in the percentage of right foot initiations between conditions. However, twice as many trials involved the right foot on the ground at bell contact in the No Ring (NR) compared to the Ring (R) condition. Stride times

were significantly greater in the R condition. When both feet were on the ground at bell contact, stride times were significantly greater than when only a single foot, left or right, was on the ground, regardless of condition. ROMs of all four joints were less in R than NR. Peak velocity was greater in R for the hip and knee, with no difference in the shoulder and less in R than NR for the elbow. Conclusion: Overall, results indicate that instructions that modify the complexity of the grasp have a significant effect on the movement patterns used to complete the overall task; primarily manifested as a more cautious gait pattern with restricted ROMs. Moreover, the upper and lower limbs appear to demonstrate a level of independent control.

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### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.12/V2

**Topic:** F.06. Posture and Gait

**Support:** NIH Grant P41 EB018783  
NIH Grant R01 NS110577  
Department of Bioengineering at University of Texas at Dallas  
Stratton VA Medical Center

**Title:** A Pre-Clinical System for Shaping Neuroplasticity

**Authors:** J. S. CARP<sup>1,2</sup>, J. RILEY<sup>4</sup>, Y. SALINAS-REYES<sup>4</sup>, D. PRUITT<sup>4</sup>, Y. CHEN<sup>1</sup>, T. M. VAUGHAN<sup>1</sup>, \*J. HILL<sup>6,3</sup>, E. MEYERS<sup>5</sup>, J. R. WOLPAW<sup>1,2,3</sup>;

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**Abstract:** The CNS is capable of change (plasticity) throughout life. This knowledge enables development of novel therapies for addressing neurological impairments. These protocols target beneficial change to a CNS site important in a behavior like walking or reach-and-grasp. The targeted change enables better practice, which in turn leads to widespread beneficial change that improves the entire behavior. Our pre-clinical development of these therapies typically entails studies with freely-moving chronically-implanted rats. These studies need specialized software to collect, evaluate, and store data continuously (24/7) and give immediate feedback (e.g., food pellet, electrical stimulation) to multiple animals concurrently. We address this need with our custom software Elizan. The first version of Elizan was written in 1984 to run on a DEC 11/34 computer; it supported concurrent interaction with and recording from up to 8 animals. It was modified in 1995 and again in 2010 to support 20 animals using Windows-based PCs with a SQL

database for 24/7 data storage. In 2024, it was made hardware-independent. Now, the University of Texas at Dallas and the National Center for Adaptive Neurotechnologies at the Stratton VA in Albany, NY are updating Elizan to use a modern programming environment (Python), and open-source data acquisition hardware (Open Ephys) that digitizes data at a skull-mounted headstage and gives digital control of stimulation and subsequent feedback based on the elicited response. This latest software upgrade provides a 24/7 interactive multi-animal platform that can automate interactions with the CNS to shape CNS plasticity according to the investigator's instructions. It provides: acquisition, processing, and storage of signals; continuous evaluation of the state of the CNS, which then triggers appropriate feedback under tight real-time constraints; and a user interface to guide setup and tuning. The system also accommodates: multiple animals at a time to give sufficient throughput; flexible configuration to support different plasticity-inducing protocols; and automation and other new features. It enables long-term 24/7 studies that facilitate development of effective new therapies for enhancing functional recovery for people with chronic neuromuscular disorders.

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## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.13/V3

**Topic:** F.06. Posture and Gait

**Support:** NIH Grant T32MH119168

**Title:** Elucidating the roles of motor function and cognitive switching in locomotor switching after stroke

**Authors:** \*N. W. BRANTLY<sup>1,6</sup>, J. CHO<sup>2,6</sup>, S. BHASKAR<sup>1</sup>, D. M. MARISCAL<sup>3,6</sup>, A. M. WEINSTEIN<sup>4</sup>, H. T. KARIM<sup>3,4</sup>, G. TORRES-OVIEDO<sup>5,6</sup>;

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**Abstract:** Locomotor switching is the ability to shift walking patterns in response to shifts between familiar environments. Sombric et al. found a correlation between locomotor switching and the ability to switch between tasks cognitively (i.e., cognitive switching) in older adults suggesting cognitive switching brain resources may support locomotor switching. Stroke survivors can have deficits in paretic leg motor function, which can cause walking impairments, including slow and unstable gait and locomotor switching deficits. However, the relationship between locomotor switching and cognitive switching and motor function post-stroke is unknown. We hypothesized that participants with better cognitive switching after a stroke would



exhibit better locomotor switching due to shared neural resources underlying these behaviors. Similarly, we hypothesized that participants with better motor function after a stroke would also exhibit better locomotor switching due to the necessity of a high-functioning motor apparatus for locomotor switching. To measure steady-state locomotor switching, we had seven participants who have had a stroke (two female, mean age 69.0 years, +/- 10.8 years SD) complete 18 abrupt switches between tied-belt and split-belt treadmill walking. These switches took place over nine trials in which the participant walked for 25 strides tied (85% of the 6-Minute Walk Test speed), 100 strides split (2:1 belt-speed ratio, symmetric about tied speed), and 25 strides tied again. We characterized steady-state locomotor switching performance as the mean of the absolute difference in step length asymmetry between the mean of the 25 strides before the switch and the 10 strides after the switch over the last five switching trials. This is a kinematic measure of how perturbed the gait is at steady state. Cognitive switching was assessed using the Dimensional Change Card Sort task from the NIH Toolbox V3. We tested the associations between locomotor switching and 1) cognitive switching and 2) motor function. We are actively collecting data toward our target N = 43 participants with stroke to detect a moderate effect size, and we have evaluated preliminary associations. We found a  $r = -0.72$  Pearson's correlation between locomotor switching and cognitive switching ( $p = 0.07$ , 95% CI = [-0.981,0.356]). We found a  $r = -0.13$  Pearson's correlation between locomotor switching and motor function ( $p = 0.79$ , 95% CI = [-0.900,0.895]). Our preliminary results suggest there may be an association between locomotor and cognitive switching, which has implications for gait rehabilitation strategies for stroke survivors.

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## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.14/V4

**Topic:** F.06. Posture and Gait

**Title:** A unified computational neuroanatomy of reaching and locomotor control

**Authors:** \*N. CHAIX-EICHEL<sup>1</sup>, N. SEETHAPATHI<sup>2</sup>;

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**Abstract:** Locomotion and reaching are seemingly distinct behaviors: locomotion is rhythmic and multi-limb, whereas reaching is discrete and single-limb. Despite these differences, both share common evolutionary origins and overlapping neural substrates, offering a powerful comparative framework for understanding motor control. While computational models have advanced our understanding of the neural control of reaching, such computational insights into supraspinal locomotor control remains sparse. In this work, we link computational models of locomotion to their neural basis by synthesizing a vast literature, drawing systematic

comparisons with reaching. We propose a novel perspective that challenges the conventional dichotomy between these behaviors: transient aspects of locomotion, such as initiation, termination, and dynamic adjustments, share strong neural similarity with reaching. Both reaching and transient locomotor events are more strongly driven by supraspinal regions, including the cortex, basal ganglia, and brainstem, whereas steady-state locomotion relies more heavily on spinal cord circuits. Our analysis also reveals that locomotion relies more heavily on long-horizon control, requiring predictive planning over extended timescales, unlike the short-horizon demands of reaching. We suggest this necessitates a distinct feedforward component that operates alongside feedback control, which is tightly linked to the functional division between transient and steady-state modes of locomotion. As a result, locomotion emphasizes proactive adaptation, while reaching relies more on reactive adaptation. Other known distinctions include locomotion's greater stability requirements and phase-dependent control, with sensorimotor integration tightly coupled to the gait cycle, features absent in reaching. Our analysis also shows that Optimal Feedback Control (OFC), which has been central to modeling reaching, does not fully capture key aspects of locomotor control. To address this, we integrate neurobiological findings with alternative frameworks like model predictive control, better suited to explain long-horizon planning in locomotion. By comparing these fundamental motor acts, we move toward a more unified understanding of how the nervous system orchestrates movement.

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## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.15/V5

**Topic:** F.06. Posture and Gait

**Title:** A Spring-Mass Hopper Platform for Neuromechanical Inquiry and Bio-Inspired Control

**Authors:** \*A. OZTURK<sup>1</sup>, O. MORGUL<sup>2</sup>, I. UYANIK<sup>3</sup>;

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**Abstract:** Legged locomotion research benefits from experimental platforms that capture the essential neuromechanical principles of agile animal locomotion. The spring-mass hopper, a functional and structural analog of animal locomotion, elegantly encapsulates natural running principles. The experimental analysis of the spring-mass hopper is crucial to understanding the sensorimotor challenges of the physical world and developing control theory applications. In our study, we developed a versatile one-legged spring-mass hopper to investigate locomotion control, focusing on stabilization with a bio-inspired strategy as a foundation for neuroscientific exploration. Our platform mimics the natural running dynamics with the active hip torque control of the spring-mass hopper, closely resembling the musculoskeletal energy injection. A planarizer mechanism enables continuous locomotion on the sagittal plane, and a real-time finite state

machine (FSM) ensures the precise event-driven coordination of locomotion phases (flight and stance). The FSM utilizes the high-resolution encoder feedback for positional measurements, mirroring how nervous systems might utilize the state-dependent coordination. Stabilization of continuous gaits is achieved through a Raibert-style controller that mimics the natural control behavior observed in animals, where the height trajectories are regulated through the energy injection and the forward velocity is controlled with the foot placement. Our results indicated that the Raibert-style controllers stabilize the locomotion with continuous multi-stride runs, where the open-loop experiments indicated the inherent open-loop instability. The successful demonstration of stable, closed-loop control of running validated that our experimental setup is a reliable, well-characterized tool for investigating the natural legged locomotion principles, and it also showed that a simplified control strategy can stabilize the complex running dynamics, a core problem solved by animal sensorimotor systems. Our work establishes a baseline with a well-characterized physical system that is suitable for future studies featuring more complex control strategies with neural networks. The utilization of neural networks for legged locomotion control will enable the exploration of high-order tasks like adaptive control and motion planning, bringing us closer to unraveling the deeper mechanisms of biological control behaviors.

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## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.16/V6

**Topic:** F.06. Posture and Gait

**Title:** Temporal Cortical Oscillatory Signatures Distinguish Falls from Recoveries Following Walking Slips among Young Adults

**Authors:** \***R. PUROHIT**<sup>1</sup>, S. WANG<sup>2</sup>, T. S. BHATT<sup>3</sup>;

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**Abstract: Background:** Falls are a leading cause of disability and often result from inadequate neuromechanical responses to sudden balance perturbations. Although biomechanical and neuromuscular factors influencing fall outcomes are well-studied, the cortical dynamics that differentiate successful recovery from falls remain poorly understood. This study aimed to identify frequency-specific cortical signatures that distinguish recoveries from falls during walking slips in young adults. **Methods:** Twenty young adults (15 female; 18-35 years) experienced an unanticipated slip while walking on an overground platform. EEG signals from a 32-channel system were band-pass filtered (0.5-60 Hz) and cleaned using artifact subspace reconstruction, independent component analysis (ICA), and dipole fitting. Oscillatory power was extracted from midline Cz for alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-60 Hz) bands.

Peak power was analyzed across four-time bins: Pre-slip (−400 to −50 ms), Early Post (0-150 ms), Mid Post (150-250 ms), and Late Post (250-400 ms). Trials were behaviorally classified as falls or recoveries, with falls defined as greater than 30% body weight supported by a safety harness. A 2 (group) × 4 (time bin) × 3 (frequency band) mixed-model ANOVA with post hoc t-tests was conducted. **Results:** There were main effects of time bin and frequency band, as well as a significant group × band × time interaction ( $p < 0.01$ ). Pre-slip cortical activity did not differ between groups and across bands. In recovery trials ( $n = 12$ ), gamma and alpha power decreased during 0-150 ms post-slip ( $p < 0.05$ ), followed by minimal increases through 400 ms, whereas beta showed minimal elevations during post-slip phases. In falls ( $n = 8$ ), beta and gamma power rose sharply beginning at 0-150 ms and peaked by 250-400 ms ( $p < 0.05$ ); alpha also showed a late-phase increase ( $p < 0.05$ ). **Conclusion:** Successful recoveries were marked by early suppression of alpha and gamma activity, suggesting attentional reallocation and motor readiness via dampened background activity and enhanced task-focused processing. In contrast, sustained beta elevation in fall trials suggests inefficient motor planning, greater error monitoring, and overrecruitment of cortical resources under threat. Overall, our findings provide a neurophysiological framework for understanding impaired balance recovery and may guide future interventions such as EEG-informed training, closed-loop neuromodulation using central or peripheral agents, or real-time fall detection systems aimed at improving cortical efficiency and reducing fall risk in vulnerable populations.

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## Poster

### PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.17/V7

**Topic:** F.06. Posture and Gait

**Title:** 50,000 trials per mouse: a scalable, automated platform for longitudinal motor behavior and neural dynamics

**Authors:** \*J. ZHONG<sup>1</sup>, R. CHOPRA<sup>2</sup>, K. B. HENGGEN<sup>3</sup>;

<sup>2</sup>Dept. of Neurol., <sup>1</sup>Washington Univ. in St. Louis, Saint Louis, MO; <sup>3</sup>Biol., Washington Univ. in St. Louis, Saint Louis, MO

**Abstract:** Many rodent behavioral assays require extensive experimenter handling and highly over-trained, cue-specific behaviors, which can obscure naturalistic motor control. To overcome this limitation, we developed an automated home-cage system that supports long-term, continuous recording. In our *ladder cage*, mice freely interact with a custom-designed ladder that separates food and water. Each voluntary ladder crossing constitutes a trial. The ladder includes ten pairs of metal rungs, each serving as a capacitive touch sensor sampled at 1,000 Hz, enabling precise detection of individual limb contacts at action-potential resolution. Videos are also recorded from both sides of the ladder for each cross. All data streams—including

electrophysiological recordings—are synchronized with millisecond precision. Our modular system also allows easy integration of additional devices. Mice without headstages average  $531.4 \pm 146.8$  crossings per day ( $n = 10$ ), and mice bearing electrophysiology headstages average  $546.2 \pm 208.6$  crossings per day ( $n = 4$ ), indicating robust engagement. We classify each crossing into eight behavioral categories—walk, trot, gallop, bound, rear, sniff under, U-turn, or mixed—using an XGBoost model trained on rung-touch patterns from the touch sensor recording; this classifier runs efficiently on a desktop. In addition, GPU-dependent approaches (e.g., DeepLabCut) can be applied to cross video segments as needed. In SOD1-mutant mice predisposed to ALS, we identified motor deficits long before the onset of clinical symptoms or detectable changes in average cross duration. Over the span of 90 days, each mouse generates ~45,000 trials, enabling longitudinal tracking of motor behavior across its lifespan. Furthermore, we examined neuronal tuning and found that learning in this unconstrained ladder paradigm differs from those in traditional forced-training tasks. This platform offers a scalable, high-resolution framework for studying the evolution of motor behavior and its neural substrates in freely behaving mice.

**Disclosures:** J. Zhong: None. R. Chopra: None. K.B. Hengen: None.

## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.18/V8

**Topic:** F.06. Posture and Gait

**Title:** Characterizing the contralateral corticospinal projections to lower extremity muscles using transcranial magnetic stimulation during walking in humans

**Authors:** N. ABDELAZIZ<sup>1</sup>, V. VEERARAGOO<sup>1</sup>, E. BLACKWOOD<sup>2</sup>, W. FENG<sup>2</sup>, A. V. PETERCHEV<sup>2</sup>, W. M. GRILL<sup>2</sup>, A. HADJIPAPAS<sup>1</sup>, \*C. C. CHARALAMBOUS<sup>2</sup>;

<sup>1</sup>Univ. of Nicosia Med. Sch., Nicosia, Cyprus; <sup>2</sup>Duke Univ., Durham, NC

**Abstract:** The corticospinal tract (CST) is integral to control of walking in humans. The “offline” use of transcranial magnetic stimulation (TMS) demonstrated that the CST is related to walking capacity, yet the CST’s real-time (“online”) contributions during walking remain unclear. Here, we extracted data from original research studies in humans that applied TMS during walking to either assess, probe, or modulate CST function “online”. We systematically searched 5 databases using predefined search strings and a search range from 1985-2025. Eligible studies applied TMS over the contralateral cortical motor areas during walking either in healthy or neurological cohorts and reported neuromotor outcomes. After identifying and screening 505 and 292 studies, respectively, we identified 27 eligible studies (1997-2022), the majority of which investigated neurotypical adults (24/27;  $N = 4$ -38; age: 20-54) and a minority examined post-stroke (2/27;  $N = 9$ -10; age: 45-66) and cerebral palsy (1/27;  $N = 10$ ; mean age: 34) adult patients. Most studies used the leg-specific stimulation coil (i.e., double cone coil; 15/27), stimulators with monophasic pulses (8/27), suprathreshold intensities (12/27), and

stimulated the right cortex (13/27). In all studies, participants walked on a treadmill (speed: 0.28-1.58 m/s; duration: 30sec-30 min) while motor evoked potentials (MEP) were recorded using surface EMG, primarily from the dorsiflexors (23/27) and plantarflexors (20/27). The MEP modulation indicated consistent phase-dependent CST excitability; MEPs of tibialis anterior (a proxy muscle of dorsiflexors) and soleus (a proxy muscle of plantarflexors) increased during swing and stance phase, respectively. Also, 8 studies demonstrated task-specific modulation during complex gait tasks. Modulation was greater in distal than proximal leg muscles (4/27). In addition to CST probing, 6 studies combined repetitive TMS with paired associative stimulation during walking; their findings demonstrated timing-dependent plasticity. In neurological cohorts, CST function was responsive to neuromodulation in stroke and was preserved in cerebral palsy. Cumulatively, the CST during walking is affected by a feedforward control (4/27) and CST-spinal reflex interactions (9/27). In summary, these findings highlight a dynamic and adaptable role of CST in gait, supporting its relevance for real-time assessment and modulation. Therefore, understanding fully the role of the CST during walking can provide valuable insights for targeted neuromodulation strategies, especially in neurological cohorts (e.g., stroke) with walking impairments (e.g., deficient foot clearance).

**Disclosures:** N. Abdelaziz: None. V. Veeraragoo: None. E. Blackwood: None. W. Feng: None. A.V. Peterchev: None. W.M. Grill: None. A. Hadjipapas: None. C.C. Charalambous: None.

## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.19/V9

**Topic:** F.06. Posture and Gait

**Support:** Lundbeck foundation R366-2021-233  
Novonordisk foundation NNF23OC0082192  
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EIC Pathfinder Open Project 101130161 - Move2Treat

**Title:** The neural topologies that orchestrate locomotion

**Authors:** \*R. W. BERG<sup>1</sup>, S. A. KOMI<sup>2</sup>, G. HOUSER<sup>1</sup>, A. WINTHER<sup>3</sup>;  
<sup>2</sup>Dept. of Neurosci., <sup>1</sup>Univ. of Copenhagen, Copenhagen, Denmark; <sup>3</sup>Dept. of Neurosci., Univ. of Copenhagen, KBH N, Denmark

**Abstract:** How does a cat gracefully walk and suddenly freeze when spotting a mouse? So far, it has been difficult to contemplate a spinal central pattern generator (CPG) capable of both autonomous generation of movement and pausing at any point while maintaining posture. To better understand the generation and pausing of motor activity, we use Neuropixels probes in the rat spinal cord during voluntary locomotion. We utilize optogenetic activation of the pedunculo-

pontine nucleus to control movement arrest. During locomotion, the neuronal manifold activity exhibits robust rotational patterns invariant to speed (Linden 2022) and topologically equivalent to a ring. Further, at the point of motor arrest this neural trajectory converges to a stable point-attractor, where it remained until the movement was resumed. Repeated instances of motor arrest covered a region of fixed-point attractors that formed a quasi-continuum. Through computational modeling, we argue that the network is a quasi-continuous region of point attractors which are contingent on specific parameters, which could be adjusted by descending input. We further suggest a structural mechanism of physical implementation. The structural mechanism entails a longitudinal projectome with a skewed Mexican hat topology, i.e. primarily local recurrent excitation and longer-range inhibition. Such a network can generate motor patterns through traveling waves, where frequency and amplitude can be controlled independently, and the rhythm is induced without requiring cellular pacemaker mechanisms. Further, the rhythm can be slowed down and stopped at a larger array of different phases by changing the properties of the spinal projectome and effectively forming a quasi-continuous attractor.

**Disclosures:** R.W. Berg: None. S.A. Komi: None. G. Houser: None. A. Winther: None.

## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.20/Web Only

**Topic:** F.06. Posture and Gait

**Title:** Spectral characteristics of postural sway in skilled athletes

**Authors:** \*E. V. KOLOSOVA<sup>1</sup>, A. V. GORKOVENKO<sup>2</sup>;

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<sup>2</sup>Bogomoletz Inst. of Physiol., Kyiv, Ukraine; <sup>2</sup>Dept. of Movement Physiol., Bogomoletz Inst. of Physiol., Kyiv, Ukraine

**Abstract:** Postural balance is maintained through the integration of sensory input from the vestibular, visual, and somatosensory systems and motor output, and is especially important in sports like sailing, where athletes must adapt to wind direction changes and yacht motion. While traditional stabilometric assessments typically focus on spatial and temporal parameters such as the area or length of the center of pressure (CoP) trajectory, spectral analysis of postural sway may reveal underlying neuromuscular strategies and adaptation mechanisms. The objective of the research was to assess the spectral characteristics of postural sway in qualified athletes in order to identify specific features and potential adaptive changes in their postural control mechanisms. Twelve skilled athletes specializing in sailing (10 men and 2 women,  $M_{age}=17.2$ ,  $SD=1.4$ ) took part in this study. Stabilometric measurements were conducted using the computerized stabiloanalyzer “Stabilan-01-2.” Two-factor analysis of variance with repeated measures considering two within-subjects factors - visual control with 2 levels (eyes open and closed) and stance complexity with 2 levels (upright stance and squat) was carried out in the

IBM SPSS Statistics 23.0. It was found that in the upright stance visual deprivation did not cause significant changes in any of the stabilometric parameters, which indicates a high level of sensorimotor adaptation in athletes and the dominant role of the proprioceptive system in postural control. Under the more challenging condition of squatting, statistically significant changes were observed compared to standing in both spatio-temporal and spectral parameters ( $p < 0.05$ ). These included an increase in stabilogram area and CoP velocity, as well as a redistribution of postural sway frequencies: the frequency of all three peaks in mediolateral sway shifted toward lower indices; the frequency of the first anteroposterior sway peak remained relatively unchanged, while the second and third peaks shifted toward higher frequencies. The upper boundary of the frequency range containing 60% of spectral power did not change for mediolateral sway, but significantly increased for anteroposterior sway, as well as the relative spectral power in the 2-6 Hz range, indicating a shift toward higher-frequency components, which may reflect the activation of fast corrective movements in the sagittal plane. The obtained results revealed specific features of postural control in athletes-sailors. Spectral analysis of postural sway is recommended as a sensitive method for assessing neuromuscular regulation of postural balance in sports practice.

**Disclosures:** E.V. Kolosova: None. A.V. Gorkovenko: None.

## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.21/V10

**Topic:** F.06. Posture and Gait

**Support:** P51OD011107  
P51OD011107-62S3  
R21AG081998

**Title:** Gait predicts aspects of cognitive performance in aging rhesus macaques (*Macaca mulatta*)

**Authors:** \*R. SUBEDI<sup>1</sup>, L. CENICEROS<sup>3</sup>, A. CRUZ<sup>1</sup>, A. CUNNINGHAM<sup>3</sup>, A. BROWN<sup>1</sup>, E. L. KINNALLY<sup>2</sup>;

<sup>2</sup>Psychology, <sup>1</sup>Univ. of California, Davis, Davis, CA; <sup>3</sup>Univ. of California Davis, Davis, CA

**Abstract:** Gait decline (decreased speed, lower step count, reduced distance traveled, slower cadence) can precede the appearance of clinical cognitive symptoms in aging populations; however, the mechanistic relationship and timing of gait and cognitive decline remain under investigation. In this study, we examined the relationship between parameters of gait and cognitive performance in 32 aging rhesus macaques (*Macaca mulatta*). The animals represent a subset of 15-20 year olds assessed via a standardized biobehavioral assessment at CNPRC. Gait was measured by extracting total distance traveled, speed, number of steps, and total time active during a walking test in an L-maze. Ethovision contour-based tracking was used to automatically



detect animal movement and measure locomotor activity. We also collected cognitive measures of working memory (preferential look task), environmental engagement (novel object interaction), and problem-solving (food-motivated puzzle apparatus). Among aging macaques, better gait parameters signaled better cognitive abilities. More steps predicted increased environmental engagement,  $F(1,30) = 4.597$ ,  $p = .04$ , and problem-solving,  $F(1,30) = 6.001$ ,  $p = .02$ , and greater total distance traveled predicted better working memory  $F(1,30) = 8.737$ ,  $p < .05$ . Age differences were apparent: older macaques showed less total physical activity,  $F(1,30) = 4.929$ ,  $p = .03$ , yet paradoxically, traveled more overall distance, potentially indicating less goal-directed movement  $F(1,30) = 9.470$ ,  $p < .05$ . These preliminary data suggest that geriatric gait changes are related to domain-specific cognitive outcomes. Building on these findings, tracking individual animals over time will provide detailed mapping of the temporal trajectories of gait changes and cognitive decline across the lifespan.

**Disclosures:** R. Subedi: None. L. Cenicerros: None. A. Cruz: None. A. Cunningham: None. A. Brown: None. E.L. Kinnally: None.

## **Poster**

### **PSTR228: Gait and Posture: Balancing Feedback and Feedforward Control**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR228.22/V11

**Topic:** F.06. Posture and Gait

**Title:** Upper-limb control demands alter lower-limb dynamics during locomotion

**Authors:** \*D. MARTINEZ DIAZ<sup>1</sup>, A. N. AKINRINADE<sup>2</sup>, E. O. HERNANDEZ<sup>3</sup>, N. DE LA CRUZ GARCÍA<sup>3</sup>, C. A. JOHNSTON<sup>2</sup>, C. S. LAYNE<sup>2</sup>;

<sup>2</sup>Dept. Hlth. & Human Performance, <sup>1</sup>Univ. of Houston, Houston, TX; <sup>3</sup>Tecnologico de Monterrey, Monterrey, Mexico

**Abstract: Introduction:** This study investigated how upper-limb task complexity demands modulate whole-body coordination during locomotion. It was hypothesized that requiring greater precision during a reach-to-grasp task would alter dynamic joint control and inter-limb coordination, reflecting adaptive motor strategies in response to task complexity. **Methods:** Twenty neurologically healthy adults (mean age =  $22.5 \pm 4.5$  years; 10 females), all right-handed and right-footed, performed 10 trials each during three randomized conditions: 1) walk-only (W), 2) walk while reaching to grasp a mechanically silenced cowbell (no-ring, NR), and 3) walk while attempting to prevent the cowbell from ringing (ring, R). The cowbell was grasped by the handle in all conditions to standardize grip aperture. Right sagittal plane joint kinematics of the hip, knee, shoulder and elbow were recorded using a validated markerless motion capture system. Time series of joint angles were segmented into individual strides using heel strike events. The stride during which the cowbell was reached was identified per trial, and mean joint-angles waveforms were computed for each joint, subject and condition across the 10 reaching strides. Two metrics were calculated: phase portrait pathlength (total trajectory traced in the

phase space over a gait cycle), capturing joint dynamic variability, and angle-angle area, capturing inter-joint coordination. Repeated-measures ANOVA was used when assumptions were met; otherwise, the Friedman test was applied. Bonferroni-corrected comparisons were conducted. **Results:** Hip and knee dynamics were significantly affected by task condition, with shorter phase portraits pathlengths in the R condition compared to NR and W. This indicates a reduced range and velocity of joint motion associated with increased upper-limb task complexity control demands. Arm phase portrait pathlength showed significant differences between R and NR. Hip-Knee area was significantly affected, with progressively reduced areas from W to NR, W to R, and NR to R. Knee-Elbow areas were significantly less in R than in W and NR.

**Conclusion:** Upper-limb task complexity modulated lower-limb joint dynamics and inter-limb coordination, with adaptations in lower-limb control, likely reflecting task-dependent redistribution of neural resources or compensatory coordination strategies. Metrics derived from phase portraits and angle-angle plots provide sensitive measures of coordination and may be useful for detecting subtle motor control changes in both healthy and clinical populations.

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## Poster

### PSTR229: Neuroethology: Sensory Systems

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.01/W1

**Topic:** G.01. Neuroethology

**Support:** Barrett Foundation

**Title:** Voltage drop across the body of *C. elegans* affects their running response to alternating current

**Authors:** \*J. YOUNG;  
Northeastern Univ., Oakland, CA

**Abstract:** When on agar to which 30V of alternating current is applied, *C. elegans* increases its movement speed and moves off of bacterial lawns (Tee et al., Genetics, 2023). The increase in movement speed could correspond to an escape behavior paired with a fear-like emotion. Currently, the mechanisms underlying this aversive response are being investigated. By doing these assays using mutants of various sizes, we have determined that there is a positive correlation between body length and electricity response. We believe this effect of length is due to the voltage drop across the body of the worm, and we performed additional experiments to test this idea. We found that increasing the voltage used in the experiment increased the running response of shorter worms more than it did to longer worms, consistent with our previous report that at higher voltages, wild type worms are unable to move (Tee et al., Genetics, 2023). Furthermore, we observed that worms are more likely to respond to the voltage when their

bodies are oriented more in parallel to the electric field, rather than perpendicular to the electric field. Both of these findings are consistent with the hypothesis that the voltage drop across the body of the worm affects its electricity response, and this is the likely reason why shorter worms respond less than longer worms. Tee LF, Young JJ, Suzuki R, Maruyama K, Kimura S, Suzuki R, Endo Y, Kimura KD. Electric shock causes a fear-like persistent behavioral response in the nematode *Caenorhabditis elegans*. **Genetics** (2023) <https://doi.org/10.1093/genetics/iyad148>

**Disclosures:** J. Young: None.

## **Poster**

### **PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.02/W2

**Topic:** G.01. Neuroethology

**Support:** McKnight Foundation  
AFOSR FA9550-23-1-0722  
NIH 1U01NS131438-01  
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**Title:** Fly odeon: A high-resolution, full-color virtual reality arena for studying fruitfly (insect) vision and navigation

**Authors:** \*D. NATESAN<sup>1</sup>, S. JEE<sup>2</sup>, K. KIM<sup>3</sup>, J. Y. LAI<sup>1</sup>, C. A. HARIMAN<sup>1</sup>, S. KIM<sup>1</sup>;  
<sup>1</sup>Molecular, Cellular, and Developmental Biol., UC Santa Barbara, Santa Barbara, CA;  
<sup>2</sup>Dynamical Neurosci., <sup>3</sup>Allosphere Res. Facility, Univ. of California, Santa Barbara, Santa Barbara, CA

**Abstract:** Insects exist in a unique visual "umwelt"—a sensory world that is shaped by their compound eyes, which are highly sensitive to motion and span nearly the entire visual field. Most insects have photoreceptors that can detect ultraviolet, blue, and green/amber. Insects use vision to orient themselves, memorize multiple landmarks, and navigate long distances. Investigating the neural basis of insect navigation requires a system that can provide naturalistic visual stimuli under controlled and restricted laboratory environments. To address this limitation, we developed a virtual reality (VR) arena with three features: 1) a full-color system tuned to the color photoreceptors of the insect eye; 2) spanning the entire visual field and capable of running at frame rates of 120 Hz; 3) simultaneous two-color imaging of neural activity. The VR arena uses four projectors to display visual stimuli on a cylindrical screen. We performed rigorous calibrations to ensure uniform brightness and seamless overlap between images from all projectors. With the aid of graphics libraries (OpenGL) and game

engines (Unity), we can provide a continuous, seamless, and naturalistic scene across the whole arena, which is updated by the insect's movement in a closed-loop manner.

The arena is primarily developed with fruit flies in mind, but is modular and can be used to study navigation in other species. It comes in three variants: a compact 330° arena (15 cm diameter & height) for physiology experiments requiring simultaneous neural recordings, a compact 360° arena for tethered behavior experiments, and a large 360° arena (30 cm diameter & height) for freely walking and flying behavior experiments. We are currently using all three variants for different types of experiments and will present the corresponding results.

Overall, the fly odeon VR arena facilitates deep investigations of the fly/insect visual system by enabling the presentation of full-color naturalistic scenes and simultaneous recording of neural activity. In addition, the integration with game engines allows us to present a rich repertoire of visual landscapes and close examinations of the neural basis of navigation in insects.

**Disclosures:** D. Natesan: None. S. Jee: None. K. Kim: None. J.Y. Lai: None. C.A. Hariman: None. S. Kim: None.

## **Poster**

### **PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.03/W3

**Topic:** G.01. Neuroethology

**Support:** NIH NICDC F31DC022188  
NIH BRAIN 1RF1NS116584-01  
NIH NIDCD 5R01DC018570-05  
NIH NIDCD 5R01DC018570-06  
Smith Family Foundation

**Title:** Hierarchical prioritization of behavior during thermal threat

**Authors:** \*E. S. DICKINSON, R. RAY;  
Yale Univ., New Haven, CT

**Abstract:** Animals must constantly navigate competing survival needs, such as feeding, sleeping, and mating, by integrating internal states with external environmental cues. While acute stressors are well established to drive rapid behavioral shifts, how behavioral priorities adjust during sustained threats remains largely unexplored. Here, we discovered that slowly changing temperatures are perceived as a persistent threat and explored how it reorganizes behavioral architecture. To achieve this, we quantified the behaviors of freely moving flies in an arena while fluctuating the environmental temperature at rates that match those most frequently observed in nature. Under stable environmental conditions, flies exhibited classic circadian-driven patterns of behavior, even across a range of temperatures ( $\pm 10^\circ\text{C}$ ) outside their preferred  $25^\circ\text{C}$ . However, when temperature fluctuates at ethologically relevant rates, behavioral

prioritization becomes more rigid, dominated by external thermal cues rather than internal circadian timing. As a result, behaviors are re-ordered by the urgency of physiological needs: for example, flies prioritize food attraction over sleep, favoring immediate survival demands over longer-term homeostatic needs. Currently, we are using behavioral genetics to identify the streams of sensory information that shift behavioral prioritization, linking sensory processing mechanisms to changes in the behavioral algorithm. Ultimately, this model will provide insight into how animals dynamically restructure behavioral priorities when coping with on-going environmental challenges.

**Disclosures:** E.S. Dickinson: None. R. Ray: None.

**Poster**

**PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.04/W4

**Topic:** G.01. Neuroethology

**Support:** NSF CRCNS 2113028

**Title:** Experimental and modeling studies of the effects of aging and changes in skeletal stiffness on force detection in insects

**Authors:** \*S. N. ZILL<sup>1</sup>, S. S. CHAUDHRY<sup>2</sup>, I. KUDYBA<sup>3</sup>, N. S. SZCZECINSKI<sup>3</sup>;  
<sup>1</sup>J.C. Edwards Sch. Med., Huntington, WV; <sup>2</sup>J. C. Edwards Sch. Med., Huntington, WV; <sup>3</sup>West Virginia Univ., Morgantown, WV

**Abstract:** Increases in stiffness of body structures often occur in growth and aging. These changes can potentially impede walking and turning movements. The effects of these changes on proprioceptive sensory signals have been less well studied. We are examining the effects of aging and skeletal stiffness on sense organs that detect forces in the legs of insects by 1) measuring exoskeletal stiffness in juvenile and adult cockroaches (*Periplaneta americana*) using an Aurora (300) dual mode lever system and 2) characterizing the responses of tibial campaniform sensilla (which encode strains in the exoskeleton) at different stages of development and sclerotization. At all stages of growth, the tibial sensilla respond vigorously to bending forces imposed as ramp and hold functions upon the tibia (with joint movement resisted). The sensitivities of sensilla in juvenile (softer cuticle) and adult (stiffer) were compared by measuring the sensory discharge frequencies in the hold phase at different levels of imposed force. Sensitivities of sensilla of juvenile animals (10th instar, pre-adult molt) were much greater to lower levels of force than adults after the succeeding, last molt. Our data indicate that the sensitivities to forces change substantially during the final stage of development. The slopes of plots of firing frequency vs. force were juvenile (slope = .617) as compared to adult cockroaches (slope = .397 adjusted for length), hardened after the single final molt, while the range of force detection increased three fold. We are planning to extend these experiments to 1) study the

specific mechanisms underlying changes in receptor sensitivities and 2) examine whether comparable changes occur in reflex activation of motor neurons to leg muscles by sensory discharges in juvenile and adult animals. These findings support the idea that the sensory systems of insects are tuned to the changes in body structure that occur in development. This tuning permits integrative processes to continue despite large, age-related changes in muscular and skeletal properties that affect the magnitude and timing of forces and movements.

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## **Poster**

### **PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.05/W5

**Topic:** G.01. Neuroethology

**Support:** NIH Grant 5K99EY035504

**Title:** The striking impact of social isolation on face cell-like neurons in a social wasp

**Authors:** \*C. M. JERNIGAN<sup>1,2</sup>, W. FREIWALD<sup>3</sup>, M. SHEEHAN<sup>2</sup>;

<sup>1</sup>Biol., Wake Forest Univ., Winston-Salem, NC; <sup>2</sup>Neurobio. and Behavior, Cornell Univ., Ithaca, NY; <sup>3</sup>Rockefeller Univ., New York, NY

**Abstract:** *Polistes fuscatus* wasps possess individually distinctive color patterns on their face, which they use to visually recognize and discriminate nestmates. Behaviorally, these wasps specialize in this visual recognition ability like humans and non-human primates. However unlike in primates, color is a critical component of this signal. Also, like humans and non-human primates, the development of this specialized ability requires social experience in these wasps. Animals who have never seen another wasp are do not discriminate among social images. Previously, we found that synaptic volumes in the lateral protocerebrum of *Polistes fuscatus* are differentially impacted by social experience. In these same brain areas, we have also found a localized physiological population of units in normally reared animals that are selective to forward-facing wasp images. We termed these forward-facing wasp selective units, *wasp cells*. These *wasp cells* show idiosyncratic tuning to different holistic faces and tend to prefer a subset of faces or specific facial features in our datasets. We now perform multichannel extracellular electrophysiology recordings in the brains of *Polistes fuscatus* wasps that have been isolated for their entire adult lives and have never seen another adult wasp. We find a striking difference in the relationship between the selectivity for forward-facing wasp images with and without internal pattern features across the brains of these animals. In normally reared animals there is a very tight relationship between a unit's selectivity for wasp shape with and without internal wasp features. In isolated animals this relationship is almost entirely gone. However, we do still find units that are selective for forward facing wasp images with and without internal wasp features,

though the degree of their selectivity and proportion of units is reduced. This suggests that there is a developmental program in *Polistes fuscatus* that produces *wasp cells* in appropriate regions of the brain and experience is not necessary for social image selectivity to develop in these circuits, though the proportion of selective units and their degree of selectivity is impacted. The normally strong relationship between wasp shape selectivity with and without internal wasp features across visual units is strongly disrupted in isolated animals. Taken together this suggests that instead of impacting the development of *wasp cells*, connectivity between these circuits responding to wasp shapes and internal wasp features may be what is shaped by social experience. We hypothesize that this connectivity between wasp feature selective units may be key for identity processing in this species.

**Disclosures:** C.M. Jernigan: None. W. Freiwald: None. M. Sheehan: None.

## **Poster**

### **PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR229.06/W6

**Topic:** G.01. Neuroethology

**Support:** Israel Foundation of Science 3382/24

**Title:** Calcium imaging in the hippocampal formation of freely behaving Japanese quails (*Coturnix Japonica*)

**Authors:** \*A. BLAU, S. ZOABI, S. BERLIN, Y. GUTFREUND;  
Neurobio., The Ruth and Bruce Rappaport research Inst. and Fac. of Medicine, The Technion – Israel Insti, Haifa, Israel

**Abstract:** Viral delivery systems—notably adeno-associated viruses (AAVs)—have revolutionized systems neuroscience by enabling cell-type-specific expression of genetic probes for long-term monitoring of neuronal activity *in vivo*. However, AAV vectors have been predominantly optimized for use in rodents, limiting their applicability in emerging non-traditional model organisms. This gap poses a significant obstacle for comparative cross-species neuroscience. In our investigations of head direction and place cells in Japanese quails, we found that commonly used AAV serotypes fail to efficiently transduce neurons in this species, underscoring the urgent need for tailored viral tools for avian models. To address this gap, we have previously engineered a unique AAV1 variant (AAV1-T593K; denoted AAV1\*) that provides moderate infection of quail neurons *in vivo*. During the course of this study, we have identified an additional Avian AAV variant. Systematic exploration of this variant shows that it exhibits very high tropism towards quail neurons and likely employs an alternative AAV infection pathway. Combining these new AAVs with GCaMP8s, we achieve continuous *in vivo* monitoring of neuronal activity over six weeks using a commercial miniscope. Preliminary data from freely behaving quails reveal that specific hippocampal neurons in quail exhibit spatially

tuned activity reminiscent of their mammalian equivalents, with distinct firing patterns correlated with direction and location. Together, our work demonstrates that overcoming species-specific barriers—through retro-engineered AAV capsids or resurrected wild-type isolates—enables chronic calcium imaging in avian models, revealing principles of hippocampal spatial coding. We provide a blueprint for adapting molecular tools to phylogenetically diverse species.

**Disclosures:** **A. Blau:** 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.; This study was supported by a grant from the Israel Foundation of Science number 3382/24. **S. Zoabi:** None. **S. Berlin:** None. **Y. Gutfreund:** None.

## **Poster**

### **PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR229.07/W7

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**Title:** Circuit architecture for directional information processing of airflow in the cricket brain

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**Abstract:** Animals process spatial information of external stimuli and exhibit goal-directed movements based on this information. However, the neural circuits that convert sensory inputs into motor outputs for directional control remain poorly understood. To clarify the overall picture of sensory-motor conversion in goal-directed behaviors, we investigated the neural circuits underlying wind-elicited escape behavior in crickets. In response to short airflow, crickets move quickly in the opposite direction to the stimulus. Crickets detect airflow using their cerci, which are abdominal mechanosensory organs. Airflow direction and velocity are first processed by local circuits within the terminal abdominal ganglion and then transmitted to the higher centers, including the brain, via ascending projection neurons. Previous studies indicated that descending signals from the brain to the thoracic ganglia are crucial for the directional control of escape behavior. These findings suggest that the brain neural circuits process airflow information and generate descending motor commands for directional movements in the wind-elicited escape



behavior. In this study, we measured firing responses of 92 brain neurons to airflow stimuli applied from three or four directions, using intracellular recording. Based on morphology, these neurons were classified into ascending neurons (AsNs, n=27), local interneurons (LINs, n=42), and descending neurons (DsNs, n=23). Brain neurons in each group exhibited distinct characteristics in their temporal firing dynamics. AsNs mainly showed transient excitatory responses. LINs exhibited diverse excitatory and inhibitory response patterns. DsNs displayed sustained and long-lasting excitatory and inhibitory responses. Response latencies followed a hierarchical order, with AsNs responding at an average of 32 ms, LINs at 43 ms, and DsNs at 58 ms, supporting a feedforward organization of sensory-motor transformation. For directional selectivity, most AsNs and DsNs preferred the posterior or the ipsilateral side to their axon. LINs showed unbiased directional tuning across the population, with individual neurons preferring different directions. Notably, several LINs and DsNs arborizing dendrites in the lateral accessory lobe exhibited high laterality. The differences in directional tuning between neuron types suggest involvement in distinct stages of directional information processing for the sensory-motor transformation. Overall, we have identified a temporally and spatially organized neural circuit that transforms airflow sensory inputs into directional motor outputs in the cricket brain.

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**Topic:** G.01. Neuroethology

**Support:** Andrews University ORCS Grant FY25 75-201160

**Title:** Exploring possible involvement of second messenger cascades in the modulation of phonotaxis in the female house cricket

**Authors:** \*B. A. NAVIA<sup>1</sup>, L. KIM<sup>2</sup>, H.-L. PARK<sup>2</sup>, A. RODRIGUEZ VELASCO<sup>3</sup>, D. N. MBUNGU<sup>4</sup>;

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**Abstract:** The ability of a female cricket to respond phonotactically to the call of a male is variable. Although a neural model for call recognition has been proposed, the elements that modulate phonotaxis are not fully understood. It has been shown that young female cricket *Acheta domesticus* can selectively recognize the male's call and as they age and their levels of juvenile hormone decreases, their selectivity for calls of conspecific males declines. We have used pharmacological agents with known modulatory effects to test the involvement of second messenger cascades in the underlying controlling mechanism of phonotactic behavior of female *A. domesticus*. Localized nanoinjections of H7 and cGMP (both known protein kinase inhibitors)

into the prothoracic ganglion of female *A. domesticus* resulted in changes in behavioral responsiveness that mirrored changes seen in the spiking pattern of an auditory neuron crucial for phonotaxis. When the females are nanoinjected with H7, they become less phonotactically responsive (compared to pre-nanoinjection). When treated with cGMP, females become more responsive to a certain range of calls (compared to pre-treatment). These results open the door to further exploring the potential role of protein kinase in the juvenile hormone pathway and its effect on phonotaxis. We have also tested the possible involvement of male pheromones as modulators for phonotaxis. When females are exposed to males immediately after the final molt, but not allowed to mate, the typical behavior expected for young females is extinguished and females become non-selective in their responses. To determine whether this behavioral change resulted from a mix of sound and pheromone exposure, females were exposed to males that were muted by clipping a single wing and their phonotactic responsiveness tested again. Preliminary results indicate a role for both sound stimuli and pheromones in mediating phonotaxis in female *A. domesticus*. Taken together, these results suggest that modulation of the neural circuitry underlying phonotactic behavior in *A. domesticus* occurs via second messenger cascades that are subject to pheromonal inputs.

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**Support:** MEXT KAKENHI Grant Number 21K06259  
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**Title:** Developmental changes in the morphology and three-dimensional arrangement of the antennal hair plates in crickets

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<sup>1</sup>Biosystem Sci. Course, Grad. Sch. of Life Sci., <sup>2</sup>Dept. of Biol. Sciences, Fac. of Sci., Hokkaido Univ., Sapporo, Japan

**Abstract:** Insects, such as crickets and cockroaches, actively scan their environment using their antennae, sensing obstacles. Sensory information regarding the location of the antenna, when it contacts objects, is necessary for this active sensing. Clusters of mechanosensory receptors called hair plates are located at the base of the antennae, which consist of the scape and pedicel, and serve as proprioceptors to report antennal movements and location to the brain. Even at the larval stage, just after hatching, larvae have antennae and use them to explore their environment, implying that the hair plates are essential from the earliest stage of development. However, little

is known about how the morphology and spatial arrangement of the hair plate sensilla change over developmental stages. This study investigated the morphology and 3D spatial distribution of hair plates in field crickets, *Gryllus bimaculatus*, from first instar through adult. With 3D coordinate-based quantification, it was revealed that the hair plate sensilla have consistent spatial patterns across individuals at the same larval stage. As the antennal base grew by molting, existing sensilla remained, and new sensilla were inserted between them to cover the sensory space. These results indicate that the spatial organization of the hair plate would be genetically determined. Presumably, this consistent organization throughout development provides reproducible patterns of sensory inputs, enabling crickets to detect the angles and direction of their antennae. Our scanning electron microscopic observation showed that the adult crickets have hair plates on the dorsal and ventral sides of the scape and on the medial and lateral sides of the pedicel, respectively. These locations suggest that the scape plates sense the elevation of the antennal flagellum, and the pedicel plates sense its horizontal azimuth. To examine spatial differences in the central projection of sensory afferents of these hair plates, we used retrograde labeling with two different fluorescent dyes. All afferents of the hair plates had axon collaterals medially in the ventral antennal mechanosensory and motor center (AMMC) of the brain and extended to the subesophageal ganglion (SOG). No apparent differences were observed in the projection patterns depending on the location of the hair plates, but the detailed morphology and position of the axon collaterals within AMMC differed from each other. These results suggest that the position of the cricket antennae is not represented topographically. Future experiments using electrophysiology and calcium imaging will clarify the neural representation of the antennal positions.

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**Title:** Characterizing Chemoreceptor Genes in the Eusocial Sweat Bee *Halictus ligatus*

**Authors:** J. FOX<sup>1</sup>, J. LEE<sup>1</sup>, A. WEBB<sup>2</sup>, C. KINGWELL<sup>3</sup>, S. KOCHER<sup>3</sup>, \*K. ASAHINA<sup>1</sup>;  
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**Abstract:** Social behaviors, ranging from simple pairwise interactions to complex group dynamics, are essential for the survival and reproductive success of many organisms. Some

species have evolved eusociality (cooperative group living with division of labor), and this transition from transient social interactions to cooperative social structure is considered one of the transformative innovations during evolution (Szathmary and Maynard Smith, 1995). However, our knowledge about the neurogenetic basis of social behavior comes from a handful of model organisms that are not eusocial. While these models have provided insight into fundamental neural mechanisms underlying social behaviors, they offer limited understanding of how cooperative social structures emerge from the ancestral, non-eusocial lifestyle. To investigate the evolution of cooperative group living, our research focuses on sweat bees (family Halictidae), a group that exhibits remarkable diversity in social behavior, with species ranging from solitary to eusocial (Schwarz et al., 2007; Jones et al., 2023). The repeated gains and losses of eusociality within this lineage offer a powerful system for exploring the genetic and neural changes that underpin transitions between solitary and social lifestyles in closely related species. Our focal species, *Halictus ligatus*, is eusocial and common across North America and Europe, making it an ideal subject for comparative studies with other *Halictus* species that differ in social organization. We focus on chemosensory systems as a window into the neural basis of social behavior in *H. ligatus*, where volatile olfactory cues can play key roles in regulating social hierarchies (Steitz & Ayasse, 2020). We combined bulk RNA-seq and long-read isoform sequencing to assemble male and female transcriptomes, and we annotated a comprehensive set of odorant receptors (ORs), gustatory receptors (GRs), and ionotropic receptors (IRs). Phylogenetic and expression analyses revealed notable sexual dimorphism in expression within the 9-exon ORs, a clade previously linked to cuticular hydrocarbon detection and social interactions (Pask et al., 2017; Legan et al., 2021), and we also identified species-specific expansions across chemoreceptors. We also observed intriguing tissue- and sex-biased expression patterns in GRs and IRs. These findings establish a powerful reference point for detailed comparative studies on chemoreceptor genes across sweat bee species, which in turn will provide entry points for neuroanatomical and functional characterization of the chemosensory systems underlying neural innovations associated with the evolution of sociality.

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**Topic:** G.01. Neuroethology

**Support:** NIDCD R01DC019341

**Title:** Exploring nucleus angularis diversity across lizard taxa

**Authors:** \*R. W. FUQUEN<sup>1</sup>, D. HAN<sup>2</sup>, C. E. CARR<sup>1</sup>;

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**Abstract:** The early Cretaceous period marks the emergence of lizards, initiating their extensive evolutionary diversification and establishment of differing auditory anatomy across families (Manley, 2002). Notable developments include the elongation of the basilar papilla and modifications to sensory hair cells. It is thought that the ancestral papilla spanned around 1 mm in length, with a tonotopic arrangement of homogenous hair cells, frequency-tuned to below 1 kHz. Lizard families are thought to have expanded their basilar papillas to varying lengths, and to have independently established higher frequency regions. This increased range of hearing may be reflected in changes to the first order auditory nuclei in the hindbrain. In both the alligator lizard (Szpir et al., 1990) and tokay gecko (Tang et al., 2012), the cochlear nucleus angularis (NA) appears to support the processing of high frequency input (>1 kHz) in a distinct rostral region. Lower frequency inputs (0.3-1 kHz) project to both caudal NA and first order nucleus magnocellularis. To further examine whether the size and organization of NA may relate to the emergence of high frequency hearing sensitivity in lizards, we quantified the organization of NA in the green iguana, golden tegu, Asian water monitor, green anole, and tokay gecko. We also included data from the alligator lizard (Szpir et al., 1990) and rat snake (Han et al., 2024). There is considerable diversity in the size of NA, which may correlate with the emergence of high frequency hearing. Reptiles without tympana such as the tuatara and rat snake lack high frequency hearing and tend to have a small NA (Han et al., 2025). Miller (1975) observed that night lizards, whiptails, and geckos possess relatively large basilar papillae along with prominent cochlear nuclei, while chameleons have comparatively modest basilar papillae and smaller cochlear nuclei. All lizards investigated had a proportionally large NA relative to the atympanate lepidosaurs studied, comparable in size to the archosaur NA, and a relatively smaller NM and NL. Of the lizards measured, the Asian water monitor and Tokay gecko had the largest NA. Furthermore, lizard NA is characterized by neuronal diversity. Szpir et al. (1990) observed that the extent to which cell types of the alligator lizard cochlear nuclei are representative of other lizard species is not known. We examined neuronal morphology and conducted regional analyses to evaluate diversity in NA in the lizards described above, considering rat snake data as well (Han et al., 2024). In agreement with Szpir et al. (1990), we conclude that NA contains several neuron types. It seems likely that these cell types are conserved among lizards.

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**Topic:** G.01. Neuroethology

**Support:** Max Planck Society junior group grant

**Title:** Beyond the Head Twitch: Establishing a Foundation for Neurobehavioral Psychedelic States in Mice

**Authors:** \*M. Y. ABD EL HAY<sup>1</sup>, A. CUKIC<sup>1</sup>, J. DAVIDSON<sup>2</sup>, A. EL HADY<sup>3</sup>, M. L. SCHÖLVINCK<sup>4</sup>, M. N. HAVENITH<sup>5</sup>;

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**Abstract:** Psychedelic substances like psilocybin have shown great promise in clinical trials for treating severe psychiatric conditions. In human studies, a positive 'set' (mindset) and 'setting' (environment) has been shown to play a crucial role in generating beneficial acute psychedelic experiences and, subsequently, positive long-term therapeutic outcomes. In contrast, these principles are largely neglected in preclinical animal research. Instead, experiments often involve stressful procedures such as sleep-time testing, forced injections, and barren environments. They also employ brief recording periods despite pharmacology suggesting longer-lasting effects. This creates a baseline state that poorly reflects clinical conditions in humans, thereby limiting our ability to understand the fundamental mechanisms of action of beneficial psychedelic experiences.

To address these issues, we implemented a low-stress, naturalistic testing paradigm in mice. Animals undergo extensive habituation, and receive either psilocybin (2 mg/kg) or a placebo via stress-minimised, voluntary, oral administration in an enriched home cage during their active phase. Following individual testing, we observed animals in habituated groups of 4 to analyse social interactions. These multi-day video and audio recordings enable us to create individualized 'behavioural dictionaries', capturing nuanced behavioural motifs.

Voluntary oral administration of psilocybin reliably induced head twitch responses (HTRs). Furthermore, our analysis revealed that in addition, psilocybin modulated diverse behavioural motifs, including social interactions among mice. These changes in the global behavioural repertoire persisted for up to five hours, significantly outlasting the typical 1.5-hour window of HTR and aligning more closely with the expected pharmacological effect of psilocybin. This shows that incorporating "set and setting" considerations as well as extended behavioural monitoring into animal experiments can uncover prolonged, nuanced effects of psychedelics, providing a more robust foundation for understanding their mechanisms and enhancing their translational power. Such comprehensive behavioural characterization under low-stress conditions establishes a crucial baseline for future neural recordings aimed at dissecting psychedelic-induced brain states more analogous to those observed in supportive human clinical settings.

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**Topic:** G.01. Neuroethology

**Title:** Sensory deprivation induces psychosis-like behaviors in rats: Effects of haloperidol and clozapine

**Authors:** M. MARTINEZ ROMERO<sup>1</sup>, E. QUINTO MORALES<sup>1</sup>, R. RODRÍGUEZ ARELLANES<sup>1</sup>, E. PÉREZ SEPÚLVEDA<sup>1</sup>, \*A. SALDIVAR-GONZALEZ<sup>2</sup>;

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**Abstract:** Schizophrenia (Sch) is considered one of the most disabling chronic mental disorders. However, the underlying brain mechanisms involved remain unclear. The Sch clinic is characterized by positive and negative symptoms. Within psychosis features are hallucinations, delusions, disorder of thinking and speech, catatonia and psychomotor agitation, all of them known as positive symptoms. On the other hand, there are negative symptoms; blunted affect, alogia, lack of motivation, social withdrawal and anhedonia. Current animal models, however, are not sufficiently effective in replicating their key features. Therefore, developing animal models for schizophrenia is crucial for a deeper understanding of the neurobiological basis of the disease. Male Wistar rats weighing 250-300 gr housed in an inverted dark-light cycle 12 to 12 hours were used. The individuals were exposed to a dark soundproof room; odors were eliminated by activated coal filter. The duration of sensory deprivation was 60 minutes divided in 15 min of exposure followed by 5 min resting. At the end the animals were tested in the open field test. The number of crossings and the number of rearings were recorded in a 5 min observation. Intraperitoneal injection of haloperidol at 1.0 and clozapine 0.5 mg/kg 30 min before the test was used. The sensory deprivation elicited increased in the number of crossings and in rearing behavior. Both haloperidol and clozapine were able to block crossings and rearing behaviors. This study reports findings indicative of psychosis-like behaviors, particularly psychomotor agitation. Additionally, we aim to induce behaviors that reflect the negative symptoms of schizophrenia.

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**Topic:** G.01. Neuroethology

**Support:** UNAM PAPIIT IA202724

**Title:** Exploration of olfactory-driven behavior in C58/J mice under a predation threat using the hole-board paradigm

**Authors:** E. LUNA CASTAÑÓN<sup>1</sup>, E. CALLADO<sup>2</sup>, E. ROCHA GONZÁLEZ<sup>3</sup>, \*O. R. HERNANDEZ PEREZ<sup>4</sup>;

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**Abstract:** □ Autism is a neurodevelopmental disorder characterized by difficulties in social communication, repetitive behaviors, and alterations in interaction with the environment. The C58/J mouse strain has emerged as a model of interest in autism-related studies, as it exhibits behaviors that resemble certain aspects of the autism spectrum, such as social deficits and repetitive behaviors. Another characteristic associated with autism is abnormalities in sensory processing. This study investigated the behavioral responses of C58/J mice in the Hole Board test, a paradigm used to analyze exploration, anxiety, and curiosity in animals through behavioral observation. Additionally, the impact of exposure to predator odor (cat urine) on these behaviors was examined. Behavioral recordings were conducted using a hole board with 16 holes. Initially, the Hole Board test was performed on day one, and the following day, the test was repeated with cat urine placed in the corner holes to detect possible behavioral changes by comparing results with and without the odor. The results showed that C58/J mice exhibited significant differences in exploration and anxiety-related behaviors compared to controls, especially after exposure to the predator odor. These findings suggest that autistic-like mice may have altered responses to environmental threat stimuli, which could help improve understanding of the underlying mechanisms of anxiety and exploration in autism models.

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**Topic:** G.01. Neuroethology

**Support:** RF1NS121919

**Title:** Visually guided obstacle avoidance in freely moving mice

**Authors:** \*M. SIDIKPRAMANA<sup>1</sup>, C. M. NIELL<sup>2</sup>;

<sup>2</sup>Inst. of Neurosci., <sup>1</sup>Univ. of Oregon, Eugene, OR

**Abstract:** Navigating through dynamic environments is a vital aspect of visual behavior. The integration of visual and self-motion cues is known to guide such locomotion, but the neural



circuits that integrate these signals are poorly understood. Mice provide a powerful model system to study neural circuits of visual processing during navigation, but there is a lack of visually guided locomotor tasks as most visual physiology in mice is done while head-fixed. To address this we developed a novel ethological visuomotor task, based on a similar human paradigm, in which freely moving mice must avoid unexpected obstacles while traversing to a goal. Our data demonstrates that mice effectively steer around an obstacle before tactile information can be sampled, suggesting that mice use vision to estimate the location of obstacles in this task. To further explore the use of vision we compared the behavior of mice in this task in light and dark contexts. In the absence of visual information, mice spend more time closer to the obstacle and perform spatially inefficient trajectories when compared to performance in the light. When visual information is available, mice perform large head movements directed toward the edge of the obstacle to steer around it, beginning at a distance of approximately 10 cm. In the dark mice continue on their initial heading at the start of each trial, often resulting in obstacle collision. To test the role of vision through the two eyes together and separately, we performed monocular eyelid suture to remove visual input from one eye. Monocular eyelid sutures increase the likelihood to make initial turns leading with the open eye. Trajectories in this direction are more spatially efficient and are more directly targeted toward the obstacle edge. Mice also made orienting head movements farther from the obstacle and had less head movements overall when initially turning to the open side. These findings on obstacle avoidance in different visual contexts suggest mice use vision to avoid obstacles and that visual information can drive motor movements for efficient route selection. This task serves as a new paradigm to study naturalistic visual behavior in mice and a basis for future physiological experiments to determine how ethologically relevant visual information is encoded during natural behavior.

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## **Poster**

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NIGMS: P20GM103650 (Cellular and Molecular Imaging core facility)  
NIH: GM103440 (Nevada INBRE)

**Title:** Sex-specific response to competing appetitive and threatening visual stimuli in mice

**Authors:** \*A. BISWAS<sup>1</sup>, T. FENG<sup>2</sup>, J. HOY<sup>1</sup>;

<sup>1</sup>Integrative Neurosci. Grad. Program, Univ. of Nevada, Reno, Reno, NV; <sup>2</sup>Dept. of Biol., Univ. of Nevada Reno, Reno, NV

**Abstract:** The optimization of hunting behavior in animals has been shaped by millions of years of evolutionary pressure, resulting in complex adaptations that balance energy acquisition against survival costs. Animals modulate their hunting behavior based on evolutionary pressures such as energy expenditure, parental role, and threat prevalence. These pressures create trade offs that manifest differently across different sexes, developmental stages and species. In this experiment, we aimed to investigate how the presence of a visual threat modulates hunting behavior in mice that first gained hunting experience as adolescents versus adulthood using a closed-loop behavioral paradigm. C57BL6/J mice with prey capture experience were exposed to a small moving ellipse-shaped prey stimulus previously shown to evoke approach behavior. We monitored mouse pose in real time and triggered an overhead looming stimulus during active approaches towards the prey stimulus. In this paradigm, we noted interesting sex and age of experience-dependent differences in behavioral responses when faced with an overhead threat during hunting. Females, regardless of age at which they gained hunting experience, were more likely to end pursuit and escape, while males persisted in pursuit, sometimes after brief arrests driven by threat presence. Further, the specific escape dynamics measured also varied by age of hunting experience and sex. We found that adult males froze for a longer duration before initiating escape, when escape occurred and had a slower maximum escape speed than adult females. Previous studies have shown that deep layers of lateral superior colliculus along with the lateral periaqueductal gray are crucial for both prey capture behavior and visual threat escape. Deep layers of the medial superior colliculus compute threat stimulus saliency with activity correlating to escape latency, while the dorsal periaqueductal gray controls escape decision and vigor with activity correlating to maximum escape speed. We therefore hypothesize that an animal's sex dictates how hunting experience alters such midbrain circuits during specific lifestages.

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U01 NS116377  
U24 MH123423

**Title:** Gaze Maps in Marmoset Hippocampus

**Authors:** \***T. J. TYREE**<sup>1,2</sup>, J. A. BOURNE<sup>3</sup>, C. T. MILLER<sup>4</sup>;

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**Abstract:** High-acuity foveal vision enables primates to actively explore visual scenes through rapid eye movements that selectively target objects and features in the environment. Yet how the brain encodes this dynamic visual sampling to form stable spatial representations remains poorly understood. Here, we test the hypothesis that the primate hippocampus constructs a visuospatial “gaze map”—a neural representation of the relative spatial relationships among multiple gaze targets—using moment-to-moment saccadic and fixation behavior as input. Using single-neuron recordings from hippocampal subfields CA1, CA3, *dentate gyrus*, and *subiculum* in head-restrained marmosets (*Callithrix jacchus*), we analyzed neural responses as animals freely explored complex visual stimuli via saccades and fixations. Preliminary analyses of neural recordings from at least 4,927 neurons revealed robust encoding of saccade direction, speed, and memory-related revisitations across hippocampal subfields, with CA3 neurons especially enriched for saccade-tuned responses. Decoding analyses confirmed that hippocampal ensembles discriminated between initial fixations and revisits to previously viewed targets, suggesting a temporally evolving spatial memory trace of gaze behavior. CA1 neurons exhibited stronger decoding of revisitation events than CA3, and saccade-modulated firing latencies differed significantly between subfields, indicating functional specialization within the hippocampal circuit. Notably, the gaze map did not persist across image presentations, suggesting scene-specific spatial encoding with hippocampal remapping across visual contexts. This study provides the first direct evidence that primate hippocampal neurons encode a visuospatial gaze map from ongoing eye movements, linking oculomotor behavior to spatial memory processing at the subfield level.

**Disclosures:** **T.J. Tyree:** A. Employment/Salary (full or part-time): Prof. Cory T. Miller. **J.A. Bourne:** None. **C.T. Miller:** 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.; R01 DC012097, R01 NS109294, R01 NS118457, 19RT0316, U01 NS116377, U24 MH123423.

## **Poster**

### **PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.18/X3

**Topic:** G.01. Neuroethology

**Title:** Quantifying mouse locomotor behavior in oral fentanyl self-administration: an ROI based descriptive statistical analysis

**Authors:** \*E. SANCHEZ<sup>1</sup>, T. APPLEBY<sup>4</sup>, S. A. SCHLEUFER<sup>2</sup>, K. COFFEY<sup>5</sup>, S. A. GOLDEN<sup>3</sup>;

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**Abstract:** Quantifying behavior in animal models has always posed challenges due to the subjective nature of manual observation and annotation. Traditional reliance on human scoring introduces variability and potential error. Recent advances in open-source, deep learning-based tools now enable objective and automated behavioral tracking and quantification. Software such as SLEAP allows for accurate pose estimation, which can be paired with platforms like SimBA to extract descriptive behavioral statistics. However, both supervised and unsupervised behavioral classification pipelines, while continually improving, still require significant effort to implement. Descriptive statistics derived from pose estimation key points, analyzed through the lens of regions-of-interest (ROIs) within a behavioral setup, potentially offer a more digestible middle ground for rapid, first pass, results. In this study, C57BL/6J mice (n = 22; males = 10, females = 12) underwent a 15-day oral fentanyl self-administration paradigm. Animals were recorded during 3-hour sessions using low-cost Arduino cameras in standard mouse operant chambers. Pose-estimation models were developed using SLEAP and DeepLabCut, and applied to video recordings to generate daily longitudinal body-point coordinate datasets spanning the acquisition and maintenance of oral fentanyl self-administrations. These data were imported into SimBA, where 13 regions of interest (ROIs) were defined around the oral fentanyl self-administration operant chamber and corresponding behavioral metrics were extracted. For each ROI, six descriptive behavioral metrics were generated. The data were organized by individual animals, allowing for comparisons and trend identification. The data displayed correlated closely to Med-PC file data. This workflow demonstrates that combining pose-estimation and ROI-associated descriptive statistics provides an objective and time-efficient method for quantifying complex behaviors in drug self-administration. It represents a strong alternative to manual annotation, and an intermediate step before ML-guided behavioral classification, with a potential for improved accessibility and implementation for non-specialists.

**Disclosures:** E. Sanchez: None. T. Appleby: None. S.A. Schleufer: None. K. Coffey: None. S.A. Golden: None.

## **Poster**

### **PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.19/X4

**Topic:** G.01. Neuroethology

**Title:** Strain and sex differences in oral fentanyl self-administration in mice.

**Authors:** \*T. R. APPLEBY<sup>1</sup>, S. SCHLEUFER<sup>2</sup>, K. COFFEY<sup>2</sup>, S. A. GOLDEN<sup>1</sup>;

<sup>1</sup>Neurobio. and Biophysics, <sup>2</sup>Psychiatry and Behavioral Sci., Univ. of Washington, Seattle, WA

**Abstract:** Substance use disorders, particularly opioid use disorder (OUD), are critical public health challenges in the United States, exacerbated by the rise of synthetic opioids like fentanyl. The neural mechanisms that drive transitions to maladaptive drug seeking behavior (i.e. recreational use to compulsive drug use, or abstinence to relapse) are poorly understood. To study the timeline of compulsive opioid seeking and consumption, we developed an oral self-administration model of fentanyl in mice. To validate model efficacy across genetically diverse populations, we tested both male and female mice using inbred C57 (male n=55, female n = 40) and outbred CD-1 mice (female n = 22, male n = 22). We show that male and female C57 mice demonstrate characteristic drug-taking phenomena during our oral self-administration experiment, including escalation of fentanyl consumption and maintenance of optimal fentanyl levels, extinction of drug-seeking behavior when reward and associated cues are removed, and reinstatement of seeking behavior when the associated cue returns. In comparison, CD-1 mice displayed a higher rate of active and inactive lever pressing from experiment outset. Female CD-1 mice showed a learning trajectory similar to C57 mice of both sexes, with an increase in active lever pressing before reaching a plateau in the final week of self administration, as well as a modest decrease in active lever pressing during extinction. In contrast, male CD-1 mice showed far more variable lever pressing throughout the self-administration experiment, from pre-training through extinction. Finally, we show that across strain and sex, mice press the active lever inversely proportional to fentanyl dosage, suggesting that mice titrate their pressing to achieve a consistent drug-induced hedonic state. Establishment of a working oral self-administration of fentanyl paradigm in mice allows us to study the neural systems on a circuit and cell type basis that underlie drug-seeking and relapse behavior, providing selective targets for addiction treatment and prevention. Future work will expand on our recently published observations that, following incubation of highly palatable food craving, non-canonical brain areas like the visual cortex show a sharp increase in Fos expression during reinstatement (Madangopal et al., 2022). We are currently pursuing similar results in our oral self administration of fentanyl model. Data will be shown from neuropixel recordings in canonical (i.e. the nucleus accumbens) and non-canonical (i.e. visual cortex) brain areas in mice across the self administration timeline.

**Disclosures:** T.R. Appleby: None. S. Schleufer: None. K. Coffey: None. S.A. Golden: None.

**Poster**

**PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.20/X5

**Topic:** G.01. Neuroethology

**Support:** NIGMS Grant R35GM146751  
NIH Small Business Innovation Research Grant R44MH140096  
NIDA Grant R01DA059374

**Title:** Synthetic modulation of brain-wide isoflurane-activated neural circuits produces anesthetic-like effects

**Authors:** \*M. H. C. NOTA<sup>1</sup>, H. LAZARO<sup>1</sup>, J. O. GAUR<sup>2</sup>, I. CAMPUZANO<sup>2</sup>, S. A. GOLDEN<sup>3</sup>, M. HESHMATI<sup>1</sup>;

<sup>1</sup>Anesthesiol. and Pain Med., <sup>3</sup>Dept. of Biol. Structure, <sup>2</sup>Univ. of Washington, Seattle, WA

**Abstract:** Over 60,000 Americans experience general anesthesia (GA) daily. Inhaled anesthetics are commonly used to produce GA, but the neural circuit mechanisms of anesthetic action remain poorly understood. Emergence from GA remains an unpredictable process with complications such as respiratory and cardiac events, delayed recovery of consciousness, agitation, delirium, and postoperative cognitive dysfunction. We previously showed that isoflurane alters brain-wide functional connectivity using viral approaches to target isoflurane-activated circuitry (Lazaro *et al.*, 2025). We now aimed to test the hypothesis that simultaneous recruitment of multiple neural networks will produce anesthetic effects using a transgenic mouse system. We first crossed R26-LSL-Gq-DREADD mice with Fos2A-iCreER<sup>2A</sup> mice to produce heterozygous-Gq-DREADDxFosTRAP2 transgenic mice and their null-DREADDxFosTRAP2 littermates. We next captured brain-wide-activated neural ensembles during isoflurane exposure, resulting in DREADD expression in isoflurane-activated cells in the Gq-DREADD-positive mice (TRAP). In Experiment 1, we tested if chemogenetic modulation of these neural ensembles would produce anesthetic-like effects using a within-between study design. We administered either the DREADD agonist clozapine-n-oxide or deschloroclozapine after TRAP and observed loss of mobility in a modified open field test, decreased coordination on a rotarod, and thermal anti-nociception in positive mice compared to null littermates. In Experiment 2, following behavioral testing, we used a modified iDisco+ procedure (Szelenyi *et al.*, 2024) to clear intact, fixed brains and immunolabel DREADD-expressing neurons with anti-HA antibody. We imaged the brains using light sheet microscopy and quantified HA expression using an Ilastik and ClearMap-based pipeline. We observed significant isoflurane-activated HA-tagged-DREADD expression in hippocampal and subcortical brain regions. In Experiment 3 ongoing studies, we are continuing to investigate the identified neuronal populations with region-specific targeted chemogenetic manipulations to better elucidate circuit-specific mechanisms of GA.

**Disclosures:** M.H.C. Nota: None. H. Lazaro: None. J.O. Gaur: None. I. Campuzano: None. S.A. Golden: None. M. Heshmati: None.

**Poster**

**PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

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**Topic:** G.01. Neuroethology

**Support:** R35GM146751  
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R37DA033396  
P30DA048736  
P50DA042012

**Title:** Brainwide genetic capture of isoflurane-induced unconsciousness

**Authors:** \***H. LAZARO**<sup>1</sup>, K. N. SCHNEIDER<sup>6</sup>, M. JIN<sup>7</sup>, A. I. BECK<sup>1</sup>, D. R. RIJSKETIC<sup>8</sup>, A. MURRY<sup>2</sup>, J. NAVARRETE<sup>10</sup>, I. CAMPUZANO<sup>11</sup>, M. H. NOTA<sup>3</sup>, N. RESSLER<sup>1</sup>, G. I. GUTIERREZ<sup>12</sup>, E. SZELENYI<sup>2</sup>, S. R. NILSSON<sup>2</sup>, C. A. DENNY<sup>13</sup>, M. R. BRUCHAS<sup>4</sup>, B. D. HEIFETS<sup>9</sup>, H. O. DE LA IGLESIA<sup>14</sup>, S. A. GOLDEN<sup>5</sup>, M. HESHMATI<sup>1</sup>;

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**Abstract:** Every day thousands of patients undergo general anesthesia. Despite the common use of anesthetic agents, mechanisms of anesthesia-induced unconsciousness and transitions in consciousness are poorly defined. An approach to manipulate brainwide circuits regulating consciousness via synthetic central nervous system activation may pave the way for more precise transitions in consciousness and reveal underlying mechanisms. Toward this goal, we leverage isoflurane anesthesia as a tool to probe consciousness at cellular resolution within the intact brain network. We chemogenetically capture brainwide isoflurane anesthesia-activated circuitry through Targeted Recombination in Active Populations (TRAP) in Fos-2a-Cre transgenic mice. In parallel, we use electrocorticography, wireless mechano- acoustic recording of peripheral physiology, and behavioral classification with SimBA to describe a synthetic state of altered consciousness generated in the absence of an anesthetic agent. We define patterns of activation under isoflurane using intact brain immediate early gene mapping combined with brainwide high density silicon probe recordings. Our data, with whole brain analysis pipelines, identifies neural activity in an unconsciousness network characterized by select nodes with increased functional activity. We provide technical resources spanning brainwide single-cell resolution maps and neurophysiologic datasets, along with an approach to further probe cellular-level mechanisms of conscious state transitions. We propose a new approach to studying the isoflurane-induced unconscious state within the intact system. Our viral-genetic brainwide approach has the potential to advance research in generating synthetic state transitions for anesthesia, analgesia, or sleep.

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**Poster**

## **PSTR229: Neuroethology: Sensory Systems**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR229.22/X7

**Topic:** G.01. Neuroethology

**Support:** P30-DA048736  
R21-DA051193  
R01-GM139850  
Innovation grant from the Cure Addiction Now Foundation

**Title:** Microdosing biased agonists to inactivate KOR - a novel strategy to treat stress-mediated disorders

**Authors:** \*C. A. NEISWANGER<sup>1</sup>, M. V. RUIZ<sup>1</sup>, K. KIMBALL<sup>1</sup>, J. H. LEE<sup>2</sup>, B. LAND<sup>1</sup>, A. BERNDT<sup>2</sup>, C. I. CHAVKIN<sup>1</sup>;

<sup>1</sup>Pharmacol., <sup>2</sup>Bioengineering, Univ. of Washington, Seattle, WA

**Abstract:** The dynorphin/kappa opioid receptor (KOR) system mediates the dysphoric effects of stress and plays a critical role in addiction vulnerability and relapse. KOR antagonists offer therapeutic promise but are limited by either poor selectivity or short duration of action. The long-acting KOR antagonist norbinaltorphimine (norBNI) produces receptor inactivation via activation of a c-Jun N-terminal kinase (JNK)/peroxiredoxin 6 (PRDX6) cascade, leading to ROS generation and depalmitoylation of G $\alpha$ i, thereby locking KORs in an inactive conformation. Here, we demonstrate that this mechanism is not unique to norBNI. Two clinically approved compounds, nalfurafine, a G protein-biased KOR agonist, and nalmefene, a partial agonist, also activate this JNK/PRDX6-dependent pathway to inactivate KOR. Using a Cre-dependent hydrogen peroxide sensor (oROS-Gr) expressed in ventral tegmental area (VTA) KOR neurons, we show that both drugs induce robust KOR-specific ROS generation in ex vivo brain slices and in vivo fiber photometry. This signaling was blocked by opioid antagonists, PRDX6 inhibition (MJ33), or JNK inhibition (JNK-IN-8), confirming pathway specificity. This process is sex-dependent, with ROS production blocked in the high-estrogen phase of estrous and restored by progesterone treatment, highlighting hormonal gating of KOR signaling. Daily microdosing with nalfurafine or nalmefene produced cumulative and long-lasting KOR inactivation, functionally mimicking norBNI. Both compounds blocked KOR-mediated antinociception, stress-induced cue aversion (in both swim stress and opioid withdrawal paradigms), and KOR-induced prolactin secretion. However, KORs mediating diuresis and pruritus remained unaffected, revealing tissue and pathway specificity of the JNK/PRDX6 mechanism. These results reveal multiple therapeutic advantages of KOR inactivation over traditional antagonism: (1) Microdosing minimizes off-target effects by reducing the need for high receptor occupancy; (2) receptor inactivation accumulates gradually, allowing for dose titration; and (3) tissue-specific engagement may preserve beneficial KOR signaling (e.g., antipruritic effects) while blocking dysphoric or stress-amplifying pathways. Together, our data redefine nalfurafine and nalmefene as KOR-inactivating agents, rather than simple agonists, and position them as viable candidates for repurposing in stress-related psychiatric and substance use



disorders. This work introduces a new avenue for tuning GPCR activity by targeting intracellular inactivation pathways, rather than traditional competitive inhibition.

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## **Poster**

### **PSTR230: Stress-Neuroimmune Interactions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR230.01/X8

**Topic:** G.03. Stress and the Brain

**Support:** State Key Laboratory of Brain and Cognitive Sciences

**Title:** Exploring the impact of social isolation on neuroimmune responses and behavior in healthy, 3xTg mice and zebrafish

**Authors:** \*X. YE, G. LEUNG, R. CHANG;

Lab. of Neurodegenerative Diseases, LKS Fac. of Medicine, Univ. of Hong Kong, Hong Kong, China

**Abstract:** Social isolation is a social problem, especially highlighted during the pandemic and among the elderly. Over three decades ago, it was identified as a key risk factor for mortality, the development of smoking habits, obesity, high blood pressure, depression, anxiety disorders, and dementia. Despite its recognized importance, the underlying mechanisms remain underexplored. Individuals experiencing social isolation often face increased susceptibility to opportunistic infections, which can exacerbate depressive symptoms. Our laboratory has demonstrated that infections and physical injuries can rapidly trigger neuroimmune responses. Therefore, we attempted to use mice and zebrafish as experimental models to investigate whether neuroimmune responses underlie the mechanism of social isolation-induced depression. Our findings indicate that after eight weeks of social isolation, 18-month-old male mice exhibited notable depressive-like behaviors, accompanied by elevated levels of complement factor 3 in the hippocampal astrocytes and an increased number of Iba1+ microglia. In contrast, socially isolated zebrafish displayed significantly lower anxiety levels. Additionally, Alzheimer's disease model mice (3xTg) that experienced social isolation showed marked increases in the phosphorylation of tau at sites 396 and 404, while overall tau protein levels remained unchanged. Collectively, these results suggest that an eight-week period of social isolation is sufficient to trigger depressive-like behavior in mice, alter neuroimmune responses, and exacerbate the progression of Alzheimer's disease.

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## **Poster**

## **PSTR230: Stress-Neuroimmune Interactions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR230.02/X9

**Topic:** G.03. Stress and the Brain

**Title:** Remapping social stress with empathy-driven social buffering

**Authors:** \*H. OH<sup>1,2,3</sup>, R. DURAND-DE CUTTOLI<sup>4,2,3</sup>, R. L. FISHER-FOYE<sup>4,2,3</sup>, T. DALY<sup>4,2,3</sup>, L. F. PARISE<sup>4,2,3</sup>, S. J. RUSSO<sup>4,2,3</sup>;

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**Abstract:** Social stress, particularly from interpersonal conflicts such as workplace bullying and school violence, is a significant risk factor for major depressive disorder (MDD). MDD remains a leading cause of disability, with current pharmacological treatments showing limited long-term efficacy. Social buffering—the alleviation of stress through positive social interactions—has emerged as a promising intervention. However, little is known about how the *condition of social buffering partners* influence recovery, as most previous studies have not addressed this factor in detail.

Here, we establish a novel behavioral paradigm to investigate the therapeutic potential of post-stress social interactions in a chronic social defeat stress (CSDS) model. Unlike prior work that primarily focused on preventative or concurrent interventions, our approach tests whether social buffering can promote recovery after CSDS-induced circuit alterations have already occurred. Moreover, we systematically examine how the emotional state of the buffering partner shapes the effectiveness of social support.

Our findings demonstrate that socially stressed mice co-housed with similarly stressed peers exhibit improved sociability and resilience, suggesting that shared emotional experiences play a crucial role in mitigating stress-induced social deficits. Building upon this paradigm, we aim to identify the underlying neural circuits mediating social buffering through circuit-level manipulations and whole-brain activity mapping. This approach will provide critical insights into the mechanisms of empathy-driven social buffering and its potential as a novel intervention for social stress-induced depression.

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### **Poster**

## **PSTR230: Stress-Neuroimmune Interactions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR230.03/X10

**Topic:** G.03. Stress and the Brain

**Support:** KAKENHI 23K06172

**Title:** Role of microsomal prostaglandin E synthase-1 in restraint stress and social defeat stress

**Authors:** \*Y. IKEDA-MATSUO<sup>1</sup>, S. AKIRA<sup>2</sup>, T. TAKAHASHI<sup>1</sup>;

<sup>1</sup>Hokuriku Univ., Ishikawa, Japan; <sup>2</sup>Lab. Host Defense, WPI Immunol. Front. Res. Ctr, Osaka Univ., Osaka, Japan

**Abstract:** Although there are many antidepressants available, most of which are drugs based on the monoamine hypothesis, and about one third of patients experience treatment-resistant depression. Thus, new therapeutic targets for antidepressants need to be discovered. We have previously reported that microsomal prostaglandin E synthase-1 (mPGES-1), a terminal inducible enzyme for PGE<sub>2</sub> synthesis, induced at lesion sites in animal models and patients with Parkinson's disease and cerebral infarction contributes to the brain inflammation and deterioration of the pathology through PGE<sub>2</sub> production. Recently, brain inflammation has been reported to be involved in not only stroke or neurodegenerative diseases, but also psychiatric disorders. In this study, to elucidate the contribution of mPGES-1 to stress-induced brain inflammation and functions, we used two mouse models of stress, acute restraint stress (RS) and social defeat stress (SDS). mPGES-1 mRNA was significantly increased after RS. Induction of mPGES-1 protein was observed in neurons in the frontal cortex (FC). PGE<sub>2</sub> in FC was also significantly upregulated in wild-type (WT) mice, but not in mPGES-1 knockout (ES1KO) mice. The inflammatory responses, such as increases in GFAP and TNF- $\alpha$ , observed after RS in ES1KO were significantly less than those in WT. In sucrose preference test (SPT), the ratio of sucrose intake after RS in WT was significantly less than that in ES1KO. In SDS model, upregulation of mPGES-1 mRNA was also observed in FC, amygdala and ventral tegmental area at Day1 and 4. Induction of mPGES-1 protein was observed in neurons in the FC at Day4. PGE<sub>2</sub> in FC was significantly upregulated at Day4 in WT mice, but not in ES1KO mice. The inflammatory responses, such as increases in Iba-1, GFAP and IL-1 $\beta$ , observed at Day10 of SDS in ES1KO were significantly less than those in WT. The ratio of sucrose intake at Day8 of SDS in WT was significantly less than that in ES1KO. Taken together, these results suggest that mPGES-1 is induced by both RS and SDS stress in FC neurons, and then contributes to brain inflammation and anhedonia through PGE<sub>2</sub> production. Thus, mPGES-1 may be a promising novel therapeutic target for treatment of depression.

**Disclosures:** Y. Ikeda-Matsuo: None. S. Akira: None. T. Takahashi: None.

**Poster**

**PSTR230: Stress-Neuroimmune Interactions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #: PSTR230.04/X11**

**Topic:** G.03. Stress and the Brain

**Support:** NIH (R01 MH119283)

**Title:** Chemogenetic activation of NTS NE neurons drives sickness behaviors in mice

**Authors:** \***R. C. DOS-SANTOS**<sup>1,2</sup>, C. FRIEDMAN<sup>2</sup>, B. L. SWEETEN<sup>2</sup>, C. E. STELLY<sup>4</sup>, L. HARRISON<sup>2</sup>, J. G. TASKER<sup>2,3</sup>;

<sup>1</sup>Univ. of South Carolina Columbia Sch. of Med., Columbia, SC; <sup>2</sup>Cell and Mol. Biol., <sup>3</sup>Brain Inst., Tulane Univ., New Orleans, LA; <sup>4</sup>Dept. of Psychological Sci., Loyola Univ. New Orleans, New Orleans, LA

**Abstract:** Sickness may be defined as a non-specific set of symptoms, such as decreased exploration, decreased food intake, and increased pain perception, that are common for several illnesses including viral or bacterial infections and cancer. Understanding the neurocircuitry responsible for the control of sickness behavior and the role of norepinephrine (NE) in this control is essential for improving overall health outcomes for chronically sick patients and may provide future avenues for pharmacological treatments of sickness symptoms. NE neurons in the nucleus of the solitary tract (NTS) are critical modulators of the physiological response to inflammation, which suggests that they may play a role in the control of sickness behaviors. To investigate the participation of the NTS-NE neurons on behavioral control we used viral vectors to induce the Cre-dependent expression of excitatory Gq designer receptors exclusively activated by designer drugs (DREADDs) in the NTS of male and female DBH-Cre mice and assessed the behavioral and endocrine responses to activation of NTS-NE neurons. After vehicle injection, males were more active than females, however, activation of excitatory DREADDs with CNO (1 mg/kg, IP) caused a significant decrease of walking, rearing and grooming activities in favor of an increase in immobility in both males and females. In addition, activation of NTS-NE neurons increased serum corticosterone when compared to vehicle injection (NaCl 0.9 %, IP). Next, we used viral vectors to induce the Cre-dependent expression of an excitatory Gq DREADD, an inhibitory Gi DREADD, or a control in the NTS of DBH-Cre mice and assessed their behavioral response to DCZ (0.1 mg/kg, IP) in a battery of behavioral tests. In the open field, activation of NTS-NE neurons decreased distance travelled and time in movement, while increased time in immobility. Food intake was also decreased by activation of NTS-NE neurons with DCZ. Half the mice submitted to activation of NTS-NE neurons were not responsive to mechanical stimulus and could not be tested on the von Frey test. When the responsive mice were analyzed, the data revealed that activation of NTS-NE neurons decreased the von Frey threshold. Meanwhile, inhibition of NTS-NE neurons did not significantly affect the behaviors assessed. Collectively, these data indicate that activation of NTS-NE neurons triggers sickness behaviors in mice, decreasing exploratory and appetitive behaviors while increasing immobility and causing allodynia. Meanwhile, inhibition of NTS-NE neurons does not affect behavior, which indicates that these neurons are not participating in the control of behavior at baseline conditions.

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**Poster**

**PSTR230: Stress-Neuroimmune Interactions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR230.05/X12

**Topic:** G.03. Stress and the Brain

**Support:** VA Merit I01BX004712  
NIMH R01 MH122954  
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NIDA R25-DA033674  
NIH NCRR P20RR016479  
Great Plains Veterans Research Foundation  
USD Center for Brain and Behavior

**Title:** Stress and Neuroinflammation are Bidirectionally Linked

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**Abstract:** Stress and neuroinflammation are closely linked in a **bidirectional relationship**. Acute and chronic stress activate the brain's immune cells, particularly microglia, leading to the release of pro-inflammatory cytokines that cause neuroinflammation. In turn, this neuroinflammation can disrupt neural circuits involved in mood and cognition, increasing vulnerability to stress and emotional disorders. This creates a **feedback loop**, where stress fuels inflammation, and inflammation heightens sensitivity to future stress. In this set of experiments, we investigated the functional interaction between stress and neuroinflammation. We first tested the effects of a stressor on brain neuroinflammatory signaling with the hypothesis that blocking calcineurin signaling with the immunosuppressant cyclosporine A (CsA) would block expression of constituents of the neuroinflammasome. Furthermore, we sought to determine if expression of a key component of neuroinflammatory signaling, the pro-inflammatory cytokine, IL-1 $\beta$ , is correlated with a stress-susceptible behavioral phenotype in the "learned helplessness" model of inescapable stress (IS) induced behavioral deficits. Finally, we hypothesized that neuroimmune activation, in and of itself, in lieu of inescapable stress, would be sufficient to develop LH-like behavioral deficits. To test this, we administered the TLR4 agonist LPS directly to brain (ICV) in place of inescapable stress and conducted behavior testing 24 h. later. Restraint stress leads to increased expression of a host of neuroinflammatory signaling molecules, many of which can be attenuated by administration of an immunosuppressant. Inescapable stress leads to significantly higher expression of the pro-inflammatory cytokine IL-1 $\beta$  in the hypothalamus of stress-susceptible (helpless) rodents than in -resilient (non-helpless) ones. Finally, inducing neuroinflammation in the absence of inescapable stress is sufficient to mimic IS-like behavioral deficits 24 hours later. Together these studies clearly demonstrate a functional bidirectional link and crosstalk between stress and neuroinflammatory signals in brain and further implicate neuroinflammatory signaling in stress-induced behaviors.

**Disclosures:** **P.J. Ronan:** None. **E. Kirschenmann:** None. **S. Rahman:** None. **T. Beresford:** None.

## **Poster**

### **PSTR230: Stress-Neuroimmune Interactions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR230.06/X13

**Topic:** G.03. Stress and the Brain

**Title:** Peripheral immune interactions at the endothelium following stress and antidepressant treatment

**Authors:** \*J. ALVAREZ<sup>1</sup>, F. CATHOMAS<sup>2</sup>, H.-Y. LIN<sup>2</sup>, L. F. PARISE<sup>2</sup>, K. CHAN<sup>2</sup>, A. RAMAKRISHNAN<sup>2</sup>, M. ESTILL<sup>2</sup>, R. L. FISHER-FOYE<sup>1</sup>, S. J. RUSSO<sup>2</sup>;

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**Abstract:** Chronic stress is a significant risk factor for the development of stress-associated psychiatric disorders, which have increasing worldwide prevalence. Clinical and preclinical studies link these disorders to alterations in the peripheral immune system, demonstrating elevated levels of pro-inflammatory immune cells and cytokines in circulation. Critically, blood-brain barrier (BBB) endothelial cells interface directly with peripheral immune cells and their released factors. Current research highlights region-specific differences in brain endothelial permeability and immune cell migration following chronic stress. However, a causal mechanistic understanding of how these changes occur in stress-responsive brain regions, including the nucleus accumbens (NAc), is not fully demonstrated. Additionally, the effects of antidepressant treatment on BBB permeability and the peripheral immune system remain insufficiently characterized. To address these gaps, 1) endothelial cell mRNA was collected from the NAc of male mice following chronic social defeat stress (CSDS) using translating ribosome affinity purification, and 2) fluoxetine was administered to male mice for four weeks following CSDS, after which we assessed BBB permeability via the Evans Blue assay. Following RNA sequencing and analysis, we observe that CSDS has a strong effect on NAc endothelial cells, such that stress-susceptible male mice display increased expression of genes associated with endothelial cell junction organization and adhesion. Current work aims to validate the upregulation of these genes and virally manipulate their expression to determine their role in immune cell recruitment to the endothelium and BBB permeability. Furthermore, stress-susceptible male mice that did not respond to four weeks of fluoxetine treatment following CSDS exhibited reduced BBB permeability compared to those that did respond to treatment. To expand upon this result, we will profile blood and brain-infiltrating immune cells from fluoxetine responders and non-responders. Together, this research will uncover unique mechanisms by which endothelial cells respond to chronic stress and highlight how available antidepressant treatments influence the BBB, providing valuable insight for the development of novel therapeutics for stress-related disorders.

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**Poster**

**PSTR230: Stress-Neuroimmune Interactions**

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**Program #/Poster #:** PSTR230.07/X14

**Topic:** G.03. Stress and the Brain

**Support:** NIH grant R01MH116026  
Animals Australia for a Kinder World

**Title:** Systemic Impacts of Vicarious Trauma Induced by Documentary Footage of Animal Suffering: Insights from fMRI, Physiology, and Monocyte Gene Expression

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**Abstract:** Witnessing trauma or suffering in others acts as a powerful stressor. In humans, observing violence inflicted on others contributes significantly to post-traumatic stress disorder, particularly in war and healthcare (Branson, 2019). Animal models showed that rodents exposed to conspecific trauma display acute inflammatory responses (Sial et al., 2016), persistent depression-like behaviors (Hodes et al., 2014), social withdrawal, and increased substance usage (Ródenas-González et al., 2023). Despite compelling evidence regarding the biological costs of witnessing trauma, little is known about how vicarious trauma affects physiological systems in healthy humans. To address this, we used an ecologically grounded paradigm using documentary footage depicting animal suffering in legal food industry practices. Participants viewed two 30-minute videos across two visits (N = 88): a vicarious trauma (VT) video showing animals suffering and a vicarious community (VC) video depicting animals' intelligent behaviors and positive human interactions. Simultaneous fMRI scanning, autonomic physiology recording, and peripheral blood collection for bulk RNA sequencing from monocytes were conducted before and after the scan. Participants reported strong negative emotions after watching VT and positive emotions after VC. These correlated with individual empathy scores. Heart rate and skin conductance were significantly elevated during VT versus VC, with heart rate increases persisting post-scan. Although the heart rate variability did not differ during viewing, it was lower during the resting state following VT. We used linear mixed-effects models to examine changes in monocyte expression of the pro-inflammatory cytokine Interleukin 1 $\beta$  (IL-1 $\beta$ ). IL-1 $\beta$  expression increased after VT, particularly in individuals with higher baseline expression. Differential gene expression analysis revealed upregulation of the peroxisomal autophagy pathway and downregulation of oxidative phosphorylation and ATP synthesis in VT compared to VC. Neuroimaging results identified brain regions, including the orbitofrontal cortex, insula,

precuneus, and striatum, where BOLD variability interacted with emotional valence and heart rate. These regions showed increased BOLD variability coupled with heart rate during negative clips, an effect absent during positive clips. Also, functional network connectivity differed significantly during VT and VC watching. In summary, this study offers a multimodal examination of the physiological impact of vicarious trauma to reveal complex biological consequences of witnessing trauma in healthy humans.

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## **Poster**

### **PSTR230: Stress-Neuroimmune Interactions**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR230.08/X15

**Topic:** G.03. Stress and the Brain

**Support:** SECIHTI grant number CF-2023-G-243  
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PAPIIT-UNAM IA200225

**Title:** IL-6 rs1800795 variant and cognitive reactivity to acute psychosocial stress in young adults: preliminary findings from an ongoing study

**Authors:** \*F. G. SÁNCHEZ GARCÍA<sup>1</sup>, F. JAUREGUI-HUERTA<sup>2</sup>, Y. K. GUTIERREZ-MERCADO<sup>3</sup>;

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**Abstract:** Genetic variation plays a critical role in shaping an individual's immunological phenotype, influencing the activity of diverse physiological systems through altered protein expression. Interleukin-6 (IL-6), a pleiotropic cytokine, acts as a key mediator with predominantly pro-inflammatory roles. The single nucleotide polymorphism (SNP) rs1800795 within the IL6 gene has been associated with altered inflammatory responses. Prior research in young Mexican university students indicated that the G:G genotype of rs1800795 is associated with higher IL-6 expression, while the C:G genotype correlates with decreased expression. This study aims to investigate the differential psychoneuroendocrinoimmunological (PNEI) reactivity to an acute psychosocial stressor (Trier Social Stress Test-Group, TSST-G) as a function of the IL6 rs1800795 variant (G:G vs. C:G genotypes) in a cohort of Mexican university students. As an initial report, this abstract focuses on findings regarding cognitive-executive functions. We are employing a quasi-experimental, comparative, cross-sectional design. Mexican university students will be genotyped for the IL6 rs1800795 polymorphism. Participants carrying the G:G and C:G genotypes will be selected and subsequently exposed to either the TSST-G (experimental group) or a non-stressful control condition. PNEI parameters are being assessed at



baseline, during, and/or post-intervention, including: immunological (serum pro- and anti-inflammatory cytokines: IL-6, TNF- $\alpha$ , IL-1 $\beta$ , IL-10), endocrine (salivary cortisol levels), autonomic (heart rate variability and respiratory rate variability), psychological (perceived stress), and executive functions (performance on standardized tasks of inhibitory control, working memory, and cognitive flexibility). Preliminary analyses, specifically focusing on cognitive outcomes obtained thus far, revealed changes in executive function performance in response to the TSST-G. Exposed students demonstrated impaired performance in tasks assessing executive domains following acute psychosocial stress. Our findings underscore the significant role of genetic variation, specifically the IL6 rs1800795 polymorphism, in modulating cognitive reactivity to acute psychosocial stress. While further comprehensive PNEI analyses (are underway, our current results contribute to the understanding of the genetic mechanisms underlying stress vulnerability as they manifest in executive functions.

**Disclosures:** F.G. Sánchez García: None. F. Jauregui-Huerta: None. Y.K. Gutierrez-Mercado: None.

## **Poster**

### **PSTR230: Stress-Neuroimmune Interactions**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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**Topic:** G.03. Stress and the Brain

**Support:** Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001  
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UFOP

**Title:** Unpredictable chronic mild stress induces anxiety like behavior and changes in VTA proteomics, associated with metabolic, immunological, and redox imbalance

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**Abstract:** INTRODUCTION: Chronic stress is a well-established public health burden. Characterized by psychophysiological responses to challenging situations, it is linked to the development of various illnesses, including mental disorders. OBJECTIVES: Evaluate anxiety-like behavior; serum metabolome, ventral tegmental area (VTA) proteome and brain redox state

of rats submitted to two weeks of unpredictable chronic mild stress protocol (UCMS). **METHODS:** Male Wistar rats (300-350g) underwent two weeks of UCMS (adapted from Burstein et al., 2018) and were then tested behaviorally (EPM, dark/light box, open field, sucrose preference). After euthanasia, brain and blood were collected for analysis. Statistical analysis was performed using GraphPad Prism, with data assessed for normality (Shapiro-Wilk) and analyzed via Unpaired T or Mann-Whitney tests. **RESULTS:** Rats subjected to 2 weeks of UCMS showed in the EPM: 1) less time in open arms (CON  $97.81 \pm 14.34$ , n=11 vs UCMS  $45.38 \pm 12.22$ ; p=0.0115); 2) fewer entries in open arms (CON  $4.909 \pm 0.5633$ , n=11 vs UCMS  $2.182 \pm 0.4635$ , n=11; p=0.0013); 3) more time in closed arms (CON  $150.9 \pm 12.92$  vs UCMS  $222.8 \pm 15.84$ ; p=0.0022). The UCMS also significantly altered metabolites: glycine (CON  $213.5 \pm 48.16$ , n=11 vs UCMS  $259.3 \pm 46.63$ , n=9; p=0.0460), myo-inositol (CON  $67.90 \pm 16.07$ , n=11 vs UCMS  $52.69 \pm 10.71$ , n=9; p=0.0125), and uridine (CON  $3.145 \pm 3.884$ , n=11 vs UCMS  $6.356 \pm 4.986$ , n=9; p=0.0321). VTA proteomics identified 4,172 proteins, with differential expression linked to phosphatidylinositol signaling and antigen processing. Redox state analysis showed increased SOD activity in the prefrontal cortex (CON  $11.78 \pm 2.935$ , n=8 vs UCMS  $15.25 \pm 2.967$ , n=8; p=0.0341) and decreased SOD in the hypothalamus (CON  $11.95 \pm 1.650$ , n=8 vs UCMS  $9.547 \pm 2.399$ , n=8; p=0.0349). In the hippocampus, UCMS reduced catalase activity (CON  $9.045 \pm 4.547$ , n=7 vs UCMS  $3.462 \pm 3.397$ , n=8; p=0.0176) and increased protein carbonyl content (CON  $14.18 \pm 4.496$ , n=6 vs UCMS  $23.96 \pm 3.3927$ , n=6; p=0.0025). **CONCLUSION:** UCMS induces anxiety-like behavior in rats, which may be associated with alterations in the redox state across different brain regions. Proteomic analysis of the VTA indicates UCMS triggers changes in the brain's inflammatory response, while serum metabolomics analysis suggests systemic metabolic reprogramming

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## **Poster**

### **PSTR230: Stress-Neuroimmune Interactions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR230.10/Y1

**Topic:** C.01. Brain Wellness and Aging

**Support:** NIH Grant R01AG078758

**Title:** Diurnal regulation of immune signaling in the choroid plexus

**Authors:** \*L. M. INCE<sup>1,2</sup>, A. ACHARYA<sup>2</sup>, A. D. GAUDET<sup>3,4</sup>, L. K. FONKEN<sup>2</sup>;

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**Abstract:** The choroid plexus (ChP) is a critical regulator of brain homeostasis; producing cerebrospinal fluid (CSF) and forming the blood-CSF barrier. The ChP is an important site for CNS immunosurveillance, facilitating immune cell entry to the ventricles via interactions between adhesion molecules expressed on the surface of immune cells, endothelial cells, and epithelial cells. Expression patterns of these migratory factors are upregulated upon immune activation to enable rapid mobilization and recruitment of immune cells to inflamed tissues. In the periphery, the circadian system regulates both homeostatic expression of adhesion molecules and inflammatory responses to promote a diurnal rhythm in leukocyte migration capacity, driven by circadian clocks in both immune cells and the vasculature. However, this has yet to be explored in the context of immune cell trafficking in the ChP. Here we show that a tissue-intrinsic circadian clock in the ChP oscillates over multiple days in culture. Bioluminescent recording of circadian phase using a clock gene-luciferase reporter mouse (mPer2<sup>Luc</sup>) shows robust oscillations with a period of approximately 24 hours. Furthermore, this circadian clock is sensitive to immune perturbations via the administration of lipopolysaccharide *ex vivo*, which shifts the circadian phase of the ChP in a time-dependent manner. As the neuroimmune environment exhibits significant changes with age, we hypothesized that circadian rhythms in the ChP from aged rodents may be disrupted and thus contribute to the excessive neuroimmune activation and immune cell infiltration observed in the aged CNS. However, ChP isolated from aged (18 months old) mice retained robust circadian rhythms *ex vivo*, indicating that any age-associated changes to ChP rhythms may be due to systemic factors rather than the ChP clock itself. To explore the impact of aging on circadian rhythms in the ChP *in vivo*, we have profiled the ChP transcriptome across a diurnal cycle (6 time points) in both young (4 months old) and aged (18 months old) C57BL/6J mice to explore the interactions between age and time-of-day in regulating ChP functions. This work highlights a novel area of circadian regulation of neuroimmune function and shed light on the capacity for ChP-targeted therapies to be modulated by time-of-day and/or age.

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## **Poster**

### **PSTR230: Stress-Neuroimmune Interactions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR230.11/Y2

**Topic:** G.03. Stress and the Brain

**Title:** Managing Threats in the Wild: Glial Activation and Corticosterone Buffering in *Rattus norvegicus*

**Authors:** \*K. G. LAMBERT<sup>1</sup>, A. NARAYANAN<sup>2</sup>, I. DILANDRO<sup>3</sup>, E. M. BYRNES<sup>5</sup>, K. BUDGE<sup>6</sup>, J. RICHARDSON<sup>4</sup>, S. C. HARTVIGSEN<sup>3</sup>, M. H. KENT<sup>7</sup>;

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**Abstract:** Given the heavy reliance on laboratory rodents in biomedical research, it's critical to compare their neurobiology with that of their wild counterparts. Our lab previously demonstrated that wild *Rattus norvegicus* exhibit elevated hypothalamic-pituitary-adrenal (HPA) activity—evidenced by increased fecal corticosterone (CORT) metabolites and larger adrenal glands—without apparent neural compromise. When controlling for body weight, wild rats exhibit heavier brains and increased cerebellar neuronal density (Jacob et al., 2022). In a second cohort, we observed region-specific neural differences in brain areas associated with vigilance, including increased glucocorticoid receptor (GR) immunoreactivity (ir) in hippocampal CA2 (stress responsiveness), higher neuronal density in the lateral habenula (threat appraisal), elevated glial density in the piriform cortex (emotional valence), and increased neuronal density in the auditory cortex (sensory vigilance). To further investigate neurobiological mechanisms of resilience in wild rats, the current study examined glial cell populations in the hippocampus of wild-caught male and female rural rats (n = 8, Rockbridge, VA) compared to laboratory controls. Wild rats exhibited significantly greater microglial-ir (associated with neural threat detection) in CA2 (p<.05), CA3 (p<.01), and dentate gyrus (p<.001). Astrocyte GFAP-ir (involved in neural energy distribution) was also increased in CA3 and dentate gyrus (p<.01 for both areas). Microglial morphology and activation states are currently being analyzed. To examine potential stress-buffering mechanisms, we analyzed corticosterone-binding globulin (CBG) levels in a separate cohort of urban wild rats (n=5, Richmond, VA). Compared to laboratory controls, wild rats had elevated serum CBG, suggesting reduced free CORT bioavailability to the brain. Altogether, these findings suggest that wild rats utilize coordinated neuroendocrine adaptations—preserving high peripheral CORT to support vigilance while protecting the brain from excess exposure. Additionally, region-specific neural profiles may further enhance emotional regulation and adaptive decision-making in dynamic natural environments.

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## **Poster**

### **PSTR230: Stress-Neuroimmune Interactions**

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**Program #/Poster #:** PSTR230.12/Y3

**Topic:** G.03. Stress and the Brain

**Support:** NSF Fellowship DGE-1938052

**Title:** Microglial gene expression in the prefrontal cortex following early life adversity

**Authors:** \*M. FANIKOS<sup>1</sup>, C. R. CODY<sup>2</sup>, H. C. BRENHOUSE<sup>2</sup>;  
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**Abstract:** The dynamic relationship between the nervous and immune systems plays an integral part in the long-term, sex-dependent impacts of adversity. Microglia, the primary neuroimmune

cell, are long-lived cells and are programmed by environmental factors early in development, which shapes their behavior throughout the lifespan. For example, neonatal bacterial infection leads to an exaggerated microglial response to immune stimulation with the bacterial toxin lipopolysaccharide (LPS) later in life. Microglia also respond to stress, and in adulthood stress primes microglia to be more reactive to subsequent LPS challenge. The mechanism of adult stress-induced priming involves glucocorticoid receptor (GR) activation and disinhibition of microglia via downregulation of the CD200 receptor (CD200R). Importantly, early life adversity (ELA) leads to dysregulation of neuroimmune signaling and function. ELA in the form of maternal separation (MS) increases expression of the cytokine TNF- $\alpha$  in the adolescent prefrontal cortex (PFC), but the cellular source of this TNF- $\alpha$  has yet to be determined. Additionally, it is unknown if ELA programs microglia via the same mechanisms as adult stress-induced priming, or if this priming is as long lasting as neonatal infection. To address if ELA alters the development of priming related genes in microglia, rats underwent MS from postnatal day (P)2-P20. Microglia were isolated from the PFC on either P11 or P21 using magnetic activated cell sorting. qPCR was used to assess expression of genes involved in the microglial priming mechanism, including GR, CD200R, and C/EBP $\beta$ . In adulthood, stress causes increased microglial expression of C/EBP $\beta$  which represses transcription of CD200R. Therefore, we hypothesize that if MS induces microglial priming via a similar mechanism as in adulthood, C/EBP $\beta$  will be upregulated and CD200R will be downregulated in MS animals. In a separate experiment, microglia will be isolated from the PFC of adolescent rats that had previously been exposed to control or MS rearing. Expression of GR, CD200R, and C/EBP $\beta$  will be measured to address the hypothesis that MS leads to long-lasting changes in stress-induced priming genes. Expression of TNF- $\alpha$  will be assessed to determine if microglia are the cellular source of increased TNF- $\alpha$  in adolescent rats following MS. Future experiments will use RNAseq as an unbiased measure to assess transcriptional changes in microglia following MS. These findings will provide valuable information about the mechanisms by which ELA leads to long-term alterations in microglial profile in the brain and how this may be related to disruptions of developing neural circuits and behavior.

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## **Poster**

### **PSTR230: Stress-Neuroimmune Interactions**

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**Program #/Poster #:** PSTR230.13/Y4

**Topic:** G.03. Stress and the Brain

**Support:** NSF Grant 211438  
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**Title:** Perineuronal net plasticity across the peripartum period and in response to gestational stress

**Authors:** \*B. LEUNER, C. DYE, M. FANKHAUSER, K. M. LENZ;  
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**Abstract:** Perineuronal nets (PNNs) are extracellular matrix (ECM) structures found throughout the brain that play a crucial role in regulating neuroplasticity. The female brain, including the prefrontal cortex (PFC), undergoes significant remodeling during the peripartum period to enable the display of maternal care but PNNs remain largely unexplored. In this study, we examined PNN expression in the PFC of late pregnant versus postpartum rats. As PNNs are known to be sensitive to stress at other times of heightened plasticity, we also examined the impact of exposure to stress during pregnancy on PNNs in the PFC. Rats (n=10/group) were exposed to chronic variable stress or control handling from gestation day (GD)7-20, then sacrificed on GD21 or postpartum day (PD)8. We found a significant increase in PNN number from GD21 to PD8. Exposure to gestational stress led to a reduction in the number of PNNs at both timepoints. The effects of stress on PNNs were confined to medial region of the PFC, with no PNN changes seen in the orbitofrontal or motor cortices. Microglia, the resident immune cells of the brain, are involved in ECM remodeling under both physiological and pathological conditions via multiple mechanisms including phagocytosis. Thus, we examined whether microglia phagocytosis of PNNs could be playing a role in the peripartum and stress-related PNN changes. This analysis revealed that microglia engulfment of PNNs decreased from GD21 to PD8. In line with this finding, there was a reduction in total C1q, a complement protein that stimulates phagocytic activity, and a decrease in C1q colocalized with PNNs at PD8 compared to GD21 as well as a negative correlation between PNN number and C1q tags on PNNs. There was no effect of gestational stress on the engulfment of PNNs by microglia at GD21 or PD8 or C1q labeling. To determine if there were stress-induced changes in microglia engulfment of PNNs preceding the reduction in the number of PNNs present at PD8, another cohort of animals (n=6/group) were exposed to gestational stress or control handling and tissue collected at PD6. At this time point, there was a significant increase in microglia engulfment of PNNs following gestational stress. Overall, these data show that: 1) decreased microglia phagocytosis of PNNs pre- to postpartum may permit increased PNNs seen in the postpartum PFC and 2) gestational stress produces a loss of PNNs in the PFC mediated by microglia phagocytosis. These results highlight the peripartum period as a window of heightened PNN plasticity within the PFC and suggest that stress disrupts extracellular matrix homeostasis through microglia-mediated mechanisms, with potential implications for maternal brain function.

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## **Poster**

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**Topic:** G.03. Stress and the Brain

**Title:** The effects of nature walk therapy on post-traumatic growth in breast cancer survivors

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**Abstract:** Breast cancer survivors often experience a range of psychological challenges, including post-traumatic stress. Post-traumatic growth (PTG), characterized by personal development following adversity, is an important aspect of recovery. Nature-based therapies, have been shown to promote psychological well-being and facilitate PTG. This study aimed to assess the effectiveness of nature walk in promoting PTG among breast cancer survivors. This quasi-experimental study evaluated the impact of nature-based walking therapy on post-traumatic growth (PTG) in breast cancer survivors using an 8-wk intervention conducted at Safari Park, Karachi. Participants were randomly assigned to either the Nature Walk Therapy Group, which engaged in guided walks with mindfulness practices, or the Standard Physical Activity Group, which continued usual activities such as walking, yoga, or gym exercises. PTG was measured using the Post-Traumatic Growth Inventory (PTGI), while mental health and physical activity levels were assessed through validated tools and wearable trackers. Post-intervention, both groups demonstrated significant improvements in PTG scores, with the Nature Walk Therapy Group showing a more considerable mean difference ( $14.9 \pm 5.8$ ,  $p < 0.001$ ) compared to the Standard Physical Activity Group ( $6.8 \pm 3.9$ ,  $p < 0.001$ ). A positive correlation was observed between time spent in nature walk therapy and changes in PTG scores. Therapy type significantly predicted PTG in the multivariable regression model ( $\beta = 8.5$ ,  $p < 0.001$ ), while age and time since diagnosis were not significant predictors. The Nature Walk Therapy Group showed greater improvements in PTG subscales, including personal strength ( $5.2 \pm 2.3$  vs.  $2.3 \pm 1.8$ ,  $p < 0.001$ ), spiritual change ( $4.2 \pm 2.5$  vs.  $2.2 \pm 1.7$ ,  $p < 0.001$ ), and appreciation for life ( $6.3 \pm 3.1$  vs.  $3.1 \pm 2.3$ ,  $p < 0.001$ ). Psychological well-being significantly mediated the relationship between therapy type and PTG ( $\beta = 0.46$ ,  $p < 0.001$ ). Growth curve analysis revealed a steeper PTG slope for the Nature Walk Therapy Group ( $14.9$  vs.  $6.8$ ,  $p < 0.001$ ), and their PTG increased more when the intervention lasted 5-8 weeks (compared to 2 weeks,  $14.9 \pm 6.3$  vs.  $7.8 \pm 4.2$ ,  $p < 0.001$ ). Nature walk therapy significantly promotes PTG in breast cancer survivors, offering a promising non-clinical intervention to support emotional recovery and personal growth. This study highlights the potential of nature-based therapies as an adjunct to traditional cancer recovery programs. Further research, including randomized controlled trials, is needed to confirm these findings and explore the long-term effects of nature-based interventions on PTG in cancer survivors.

**Disclosures:** S. Noushad: None. S. Ahmed: None. Y. Saleem: None.

**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.01/Y6

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** P500PB\_211149  
U19 NS123717  
R01DK126740

**Title:** Locomotion-associated transients in brain energy metabolism in awake mice

**Authors:** \*P. MACHLER<sup>1</sup>, Z. KU<sup>2</sup>, Y. NASU<sup>3</sup>, J. S. MARVIN<sup>4</sup>, D. KLEINFELD<sup>1</sup>;  
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<sup>4</sup>Janelia Farms Res. Ctr., Ashburn, VA

**Abstract:** Neurovascular (NVC) and neurometabolic coupling (NMC) are foundational concepts that have been assumed to reflect local energy demands from neuronal activity and are used to interpret functional magnetic resonance imaging (fMRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET) signals. One aspect of this interpretation concerns aerobic glycolysis (AG), where glucose is broken down to produce lactate although oxygen is readily available. Here we address two aspects of AG. The first concerns the dependence of AG on behavioral state. Early studies, using microdialysis and substrate-selective electrodes, and more recent studies with substrate-specific optical probes, find evidence for a systemic increase in AG in the brain with arousal, as indexed by locomotion, pupil dilation, and/or elevated norepinephrine (NE) (Zuend, M. et al. Nature 2020). The second aspect of inquiry concerns the spatial aspect of AG. Primarily in vitro and in situ experimental results established the possibility of a localized cell-by-cell variation in AG, e.g., by the astrocyte-neuron lactate shuttle (ANLS) model (Pellerin, L. & Magistretti, P. J. PNAS 1994). We revisit past claims on the nature of AG using state-of-the-art optical probes to measure extracellular D-glucose, L-lactate, and NE dynamics in awake mice, as imaged by both widefield microscopy and adaptive optics / two-photon microscopy. This allowed us to map calibrated metabolite concentrations throughout the depth of cortex and specifically address the issue of localized versus global changes in brain AG. Using novel, fast-response membrane tagged L-lactate (ReLACCO3.1) and D-glucose (iGlucoSnFR2) sensor, and a sensor of [NE] (GRABNE2h), we observed that both D-glucose and L-lactate were evenly distributed across the extracellular space, with no significant localized depletion or accumulation during spontaneous neuronal activity nor increased activity induced by vibrissa stimulation. Further, during arousal, we detected the signature of aerobic glycolysis as a global increase in extracellular L-lactate and a decrease in D-glucose. These changes in substrate lagged surges in [NE] by about 10 s and peaked at 3 minutes after the onset of arousal . Notably, arousal-linked changes in D-glucose and L-lactate occurred independently of local synaptic or calcium activity and therefore cannot be explained with an ANLS model. Our data suggests that brain AG is modulated globally by neuromodulatory systems rather than driven by local energetic demands. We propose a model wherein arousal-related neuromodulation triggers a brain-wide metabolic shift to meet anticipated energy requirements.

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**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H



**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.02/Y7

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH 1R01NS126920

**Title:** Cortical ATP levels under normal conditions and when functional hyperemia is blocked

**Authors:** \*O. B. OJO<sup>1</sup>, K. XIE<sup>1</sup>, J. A. FILOSA<sup>1</sup>, F. L. BARROS<sup>2</sup>, P. J. O'HERRON<sup>1</sup>;

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**Abstract:** Adenosine 5'-triphosphate (ATP) serves as the primary energy currency of cells, playing a crucial role in various cellular activities. Functional hyperemia ensures that the delivery of oxygen and nutrients to active neurons meets their energy needs, thereby maintaining sufficient ATP levels and promoting optimal cortical function. Nevertheless, studies indicate that functional hyperemia might exceed the tissue's actual requirements. Consequently, the extent to which increased blood flow is crucial for preserving healthy neural function remains unclear. This study tracked real-time ATP levels in the visual cortex of mice before, during and after the blockage of functional hyperemia. A novel opsin mouse model was utilized to control vessel diameter while monitoring hemodynamic activity and ATP levels with two-photon microscopy. Adeno-associated viral (AAV) vectors carrying the Förster resonance energy transfer (FRET)-based sensor ATeam 1.03<sup>YEMK</sup> were injected into the mouse's primary visual cortex to measure ATP levels in neurons and astrocytes. Functional hyperemia was activated by visual stimulation and blocked by optogenetic activation of vasoconstriction. The results demonstrate the dynamic changes in ATP levels dependent on visual processing in neurons and astrocytes, both with and without functional hyperemia. This study offers valuable insights into the complex relationship between neural activity, energy demand, and supply.

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**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.03/Y8

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH K00 NS118713  
NIH U01 DA058527  
NIH R01 DA052859  
NIH R00 DA044838

**Title:** Dietary stressors and sex exacerbate the impact of antiretroviral prophylaxis use on the brain metabolome

**Authors:** \*C. J. WHITE<sup>1</sup>, A. S. PRICE<sup>2</sup>, H. N. WILKINS<sup>3,1</sup>, A. N. ELLISON<sup>4,1</sup>, S. A. KNERLER, Jr<sup>1</sup>, D. W. WILLIAMS<sup>1</sup>;

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**Abstract:** Antiretroviral therapies (ARTs) are used as a means of primary prevention for human immunodeficiency virus (HIV) through pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) by significantly reducing the risk of transmission of HIV and its associated neurologic outcomes such as neurocognitive impairment mood disorders, and brain atrophy. Despite improving quality of life and decreasing HIV transmission risk, ARTs are known to alter peripheral and brain metabolism. The integrase inhibitor dolutegravir (DTG), which is commonly prescribed in contemporary ART regimens contributes to neuroinflammation, neural tube defects, and changes in glucose metabolism. However, the direct impact of modern ARTs on brain metabolism, under the duress of dietary stressors such as high-fat diet or acute caloric fasting, commonly experienced in populations of people without access to healthy foods, are not well characterized. To evaluate the impact of dietary metabolic duress and HIV prophylaxis on brain metabolism, we performed global metabolomics on frontal cortex from two cohorts: 1) mice that have been placed on a 10-week high-fat (60% fat) compared to low-fat (10% fat) diets and 2) a second cohort of mice include those that were subjected to a 24-hour fast compared to controls that each have received daily oral gavages of combined antiretroviral therapy (DTG, emtricitabine, tenofovir disoproxil fumarate) akin to human HIV prophylaxis treatment for 2-weeks. We determined that the impact of ART on the brain metabolome is significantly impacted by diet and sex. Male mice subjected to two-weeks of oral ARTs and 24-hours of fasting compared to male mice subjected to two-weeks of vehicle and 24-hours of fasting experienced increases in endocannabinoids, acylcholines, phosphatidylcholines. Phosphatidylethanolamines, phosphatidylcholines, phosphatidylinositols, and lysophospholipid were altered 3.01 to 1.27-fold. Male mice subjected to two-weeks of oral ARTs and 10-weeks of high-fat diet compared to vehicle controls had elevated endocannabinoids and lysophospholipids ranging from 3.18 to 2.00-fold. Furthermore, chow diet-fed males treated with ART had decreased phospholipids ranging from 0.60 to 0.79-fold and glucose metabolites ranging from 0.39 to 0.84-fold. Overall, changes in the brain metabolome due to oral ART use was most exacerbated in males and by 24-hour fasting, with significant yet comparably less differences due to high-fat diet. These data suggest that ART prophylaxis may predispose the brain to metabolic changes that may contribute to neurologic complications especially in males subjected to a dietary challenge.

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**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.04/Y9

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** Grant-in-Aid for Young Scientists from the Japanese Society for  
Promotion of Science 21K16368

**Title:** N-lactoyl-phenylalanine suppresses hypothalamic inflammation induced by high-fat diet

**Authors:** \*T. IDE<sup>1</sup>, T. SATO<sup>3</sup>, M. SUGIYAMA<sup>1</sup>, K. ASAI<sup>1</sup>, L. FU<sup>2</sup>, M. KUNO<sup>1</sup>, T. TAKEDA<sup>1</sup>, H. TAKAGI<sup>4</sup>, R. BANNO<sup>2</sup>, H. ARIMA<sup>1</sup>;

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**Abstract:** N-lactoyl-Phenylalanine (Lac-Phe) is a metabolite produced during physical exercise. It is a modified amino acid biosynthesized from lactate and phenylalanine, and is generated by CNDP2-positive cells, including macrophages, monocytes, and immune or epithelial cells found in various organs. In mouse studies, pharmacological doses of Lac-Phe did not affect energy balance under normal chow diet conditions, but significantly suppressed obesity induced by high-fat diet (HFD) intake. However, the molecular mechanisms underlying this anti-obesity effect during HFD consumption remain unclear. It is known that saturated fatty acids in HFD activate microglia in the hypothalamus, inducing inflammation in the arcuate nucleus (ARC), thereby impairing leptin and insulin signaling in hypothalamic neurons. This disruption of central energy homeostasis contributes to the development of obesity. Based on this background, we examined the hypothesis that Lac-Phe has anti-inflammatory effects in the hypothalamus under HFD conditions. Male C57BL6J mice aged 8-9 weeks were divided into three groups: a normal chow diet group (NCD), an HFD-fed group (HFD), and an HFD-fed group treated with Lac-Phe (50 mg/kg/day, intraperitoneally) (HFD + Lac-Phe). HFD and Lac-Phe were administered for 3 days. After the experiments, ARC was dissected, and mRNA expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) was evaluated and compared among the three groups. In a separate experiment, male C57BL6J mice aged 8-9 weeks received intracerebroventricular injections of either phosphate-buffered saline (PBS), TNF- $\alpha$  ( $10^{-8}$  M), or TNF- $\alpha$  ( $10^{-8}$  M) + Lac-Phe (10 or 100 ng). Sixty minutes post-injection, TNF- $\alpha$  mRNA expression in the ARC was assessed and compared among groups. TNF- $\alpha$  mRNA expression in the ARC was significantly increased in the HFD group compared to the NCD group, whereas the HFD + Lac-Phe group showed no significant difference from the NCD group. Furthermore, intracerebroventricular injection of TNF- $\alpha$  significantly elevated TNF- $\alpha$  mRNA levels compared to PBS, but this increase was significantly attenuated by co-administration of Lac-Phe. These results demonstrate that Lac-Phe exerts anti-inflammatory effects in the hypothalamus and suggest that the suppression of ARC inflammation may be a key mechanism underlying its anti-obesity effects under HFD conditions.

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**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.05/Y10

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** DP1DK143574

**Title:** Hypothalamus preoptic area stimulation evokes a conserved torpor-like state in non-torpid mammals

**Authors:** \*L. YANG, D. ZHANG, J. YUAN, Y. YANG, Y. YUE, H. CHEN;  
Washington Univ. in St. Louis, Saint Louis, MO

**Abstract:** Torpor exemplifies the brain's capacity to drive systemic metabolic suppression through coordinated neural control of energy balance and thermoregulation. Synthetic torpor, which mimics the key feature of natural torpor—hypometabolism—has been achieved by activating specific neuron types in torpid species like mice. However, inducing synthetic torpor in non-torpid mammals remains challenging, partly due to limited understanding of whether the underlying neural mechanisms are conserved across species. To address this, we developed a non-invasive neuromodulation approach—focused ultrasound (FUS)—to evoke a torpor-like state in non-torpid rats. FUS enables precise, reversible activation of the preoptic area (POA) without genetic or pharmacological manipulation, providing a unique opportunity to test evolutionary conservation of synthetic torpor circuits and identify neuron types involved in metabolic suppression. Male and female Wistar Han IGS rats (5-7 weeks old) were used. A baseplate was attached to each skull to enable precise ultrasound targeting of the POA in freely moving animals. Rats were also implanted with telemetry sensors (TSE Systems) to monitor core body temperature ( $T_{\text{core}}$ ). Oxygen consumption ( $\text{VO}_2$ ) was measured using an OxyMax sensor (Columbus Instruments). Sham controls underwent identical procedures without FUS stimulation. Approximately 90 minutes after stimulation, brains were collected for RNAscope or safety assessment. We found that FUS stimulation significantly decreased  $\text{VO}_2$  ( $-25.24 \pm 2.53\%$ ,  $n = 9$ ) and  $T_{\text{core}}$  ( $-0.98 \pm 0.20^\circ\text{C}$ ,  $n = 7$ ) compared to sham controls ( $\text{VO}_2$ :  $-3.30 \pm 1.78\%$ ,  $n = 17$ ;  $T_{\text{core}}$ :  $-0.02 \pm 0.04^\circ\text{C}$ ,  $n = 6$ ). RNAscope analysis revealed elevated *Fos* expression in the POA of FUS-treated animals ( $9.15 \pm 1.15\%$ ,  $n = 8$ ) versus controls ( $3.07 \pm 1.15\%$ ,  $n = 6$ ). A higher portion of c-Fos positive neurons co-expressing *Vglut2* ( $38.82 \pm 4.17\%$ ,  $n = 9$ ) compared to *Vgat* ( $20.86 \pm 3.12\%$ ,  $n = 9$ ). These data suggest predominant recruitment of glutamatergic neurons in FUS-induced torpor in rats, consistent with previous findings in mice. Single-nucleus RNA sequencing (snRNA-seq) was conducted to identify potential neuron types regulating synthetic torpor in rats. Immunohistological analysis revealed no tissue damage or inflammation,

and no sex differences were observed. These findings establish FUS as a safe, non-invasive method to induce synthetic torpor in non-torpid mammals, indicate conservation of torpor-regulating neurons across species, and support future human translation.

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## **Poster**

### **PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.06/Web Only

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Title:** The Impact of Sleep Deprivation on Hypothalamic Feeding Circuits

**Authors:** \*A. MALDONADO RODRIGUEZ<sup>1</sup>, R. WANG<sup>2</sup>, Y. PENG<sup>2</sup>;

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**Abstract:** Sleep loss alters metabolic homeostasis and feeding behavior, but the impact on specific hypothalamic hunger pathways remains unclear. Agouti-related peptide (AgRP) neurons in the arcuate nucleus (ARC) play a crucial role in regulating food intake and energy balance. To determine whether sleep deprivation activates AgRP neurons and alters the expression of orexigenic neuropeptides. Adult AgRP-Cre/Ai9 mice, which express tdTomato in AgRP neurons, were used to visualize cell-specific activation in response to sleep deprivation. Mice were divided into four groups: control (fed and slept), fasted, 24-hour sleep-deprived, and combined fast and sleep-deprived. C-Fos immunohistochemistry was used to assess neuronal activity in AgRP neurons. In another experiment using wild-type mice, Quantitative PCR (qPCR) was performed to determine the gene expression of AgRP, NPY, POMC, and CART in ARC tissue in SD and control mice. In control mice, AgRP neurons showed limited c-Fos expression. Sleep deprivation significantly increased c-Fos colocalization in AgRP neurons compared to controls, indicating elevated neuronal activation. qPCR revealed that AgRP and NPY mRNA levels were significantly upregulated following SD and were highest in the combined sleep + food-deprived group. Expression of POMC and CART remained unchanged. Sleep deprivation robustly activates AgRP neurons and upregulates orexigenic gene expression in the hypothalamus, independent of food intake. These findings suggest that insufficient sleep directly engages hypothalamic circuits that promote hunger, potentially contributing to altered energy balance and increased food drive during sleep loss.

**Disclosures:** A. Maldonado Rodriguez: None. R. Wang: None. Y. Peng: None.

## **Poster**

### **PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.07/Y11

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH R01 DA038599  
NIH T32-DA007281

**Title:** Identifying a neurochemical signature of the paraventricular nucleus of the thalamus that predicts individual variability in cue-reward learning

**Authors:** \*B. A. RAMOS<sup>1</sup>, M. DAHER<sup>1</sup>, R. T. KENNEDY<sup>2</sup>, S. B. FLAGEL<sup>3</sup>;  
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**Abstract:** To examine the neurochemical correlates that may render one more susceptible to psychiatric disorders, we use an animal model that allows us to capture a “neurobehavioral endophenotype” of relevance. When exposed to a Pavlovian conditioned approach (PavCA) paradigm consisting of lever-cue presentation followed by reward delivery, rats learn the cue-reward relationship and attribute predictive value to the lever-cue, but a subset of rats, sign-trackers (STs), also attribute incentive value to the lever-cue. Relative to goal-trackers (GTs), who primarily attribute predictive value to the lever-cue, STs are also more impulsive, have attentional deficits, and show greater reinstatement of drug-seeking behavior. The behavior of STs is thought to result from dominance of subcortical systems, whereas that of GTs derives from engagement of cortical systems. The paraventricular nucleus of the thalamus (PVT) has emerged as a key neural node that may differentially integrate subcortical and cortical input in STs and GTs and, in turn, guide behavior. Utilizing microdialysis with liquid chromatography-tandem mass spectrometry (LC-MS/MS) we characterized multiple neurotransmitters, metabolites, and energy molecules in the PVT. Microdialysis sampling occurred prior to the 1<sup>st</sup> session of PavCA and the day after the last (5<sup>th</sup>) session of PavCA. Rats were characterized as STs, GTs, or intermediate rats (INs; i.e., those that vacillate between sign- and goal-tracking behavior) based on their PavCA behavior. Relative to other behavioral phenotypes, STs tend to exhibit a greater increase in concentration of multiple neurochemicals from pre-PavCA (i.e., prior to learning the cue-reward relationship) to post-PavCA (i.e., after the behavioral phenotype is established). This includes dopamine and norepinephrine metabolites, such as 3,4-Dihydroxyphenylacetic acid (DOPAC) and Normetanephrine (NM), respectively. There was also a significant positive correlation between glucose concentration in the PVT and the PavCA index used to categorize behavioral phenotypes, with greater levels of glucose (pre-PavCA) in STs. Mixed linear regression models revealed clusters of neurochemicals in the PVT under baseline conditions that could predict the PavCA index, with significant contributions from glucose, dopamine and norepinephrine metabolites, and amino acid neurotransmitters. This research has identified a neurochemical signature that may predispose an animal to a form of associative learning that promotes maladaptive behavior and could therefore aid in the development of novel therapeutic targets for the treatment of psychiatric disorders.

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**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.08/Y12

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

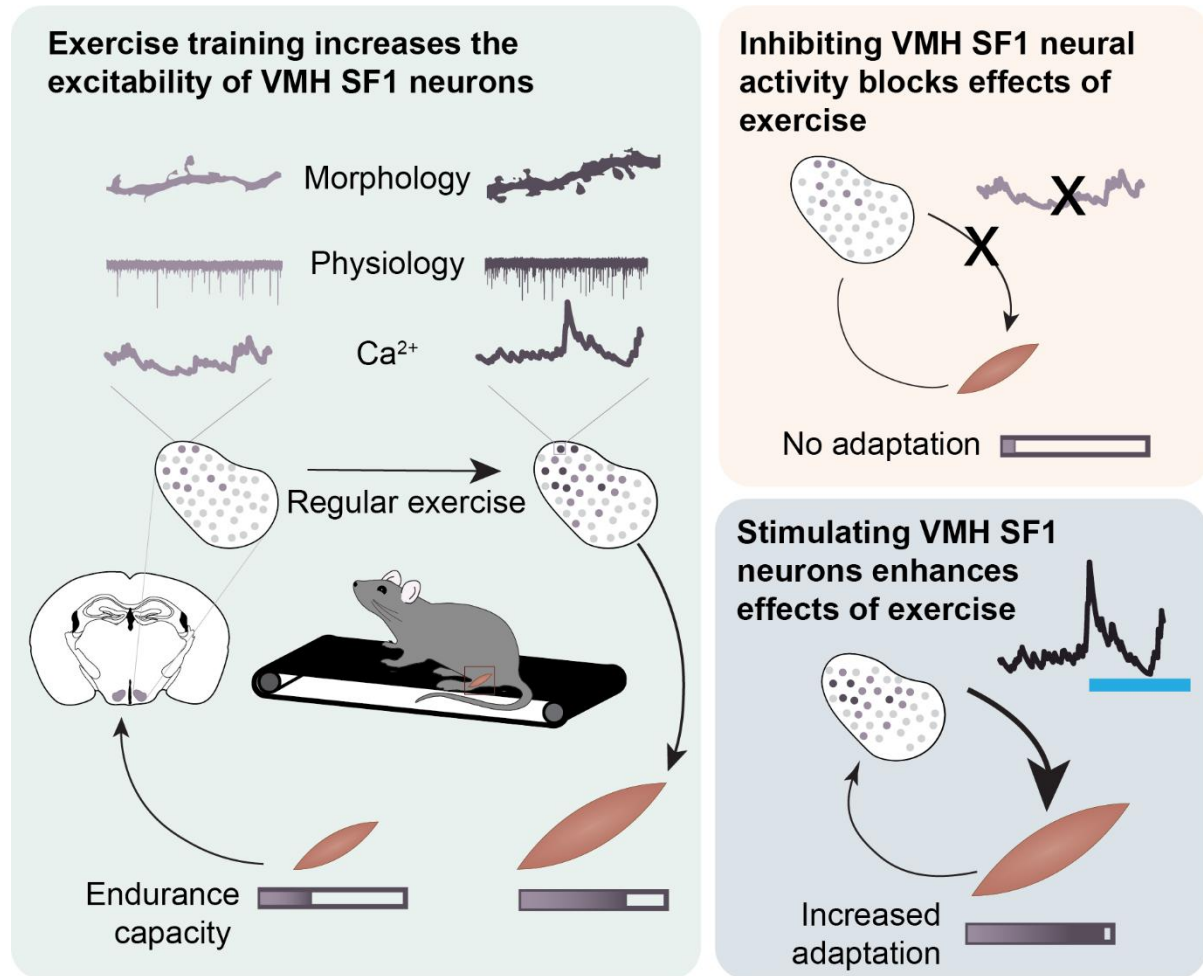
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NIH Grant F32 DK 131892  
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NSF GRFP DGE-1845298

**Title:** Exercise-induced activation of ventromedial hypothalamic neurons mediates improvements in endurance

**Authors:** \*M. KINDEL<sup>1</sup>, R. J. POST<sup>2</sup>, J. CARTY<sup>3</sup>, N. GOLDSTEIN<sup>4</sup>, J. K. ELMQUIST<sup>6</sup>, E. BLOSS<sup>7</sup>, J. BETLEY<sup>5</sup>;

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## Abstract:



Regular exercise produces robust physiological benefits and is the leading lifestyle intervention for human health. The benefits from exercise training result from the remodeling of skeletomuscular, cardiovascular, metabolic, and endocrine systems. Here, we show that exercise-induced activation of the central nervous system is also essential for mediating subsequent changes in endurance performance and metabolism in female and male mice. Ventromedial hypothalamic steroidogenic factor-1 (SF1) neurons are activated following exercise ( $n = 93$  cells, 4 mice) and this post-exercise activation is further increased by repeated exercise. Exercise training increases intrinsic excitability ( $n = 12$ -19 cells/group) and increases the density of excitatory synapses on SF1 neurons ( $n = 26$ -31 branches/group), suggesting that exercise history is encoded through hypothalamic plasticity. Blocking SF1 neuron output in a Cre-dependent manner in SF1-Cre mice prevents exercise-induced endurance gains and metabolic changes ( $n = 15$  mice) relative to Cre-negative littermates ( $n = 16$  mice). Conversely, optogenetic stimulation of opsin-expressing SF1 neurons following exercise enhances gains in endurance ( $n = 12$  mice) relative to eYFP-expressing controls ( $n = 12$  mice). These results demonstrate that exercise-induced hypothalamic SF1 neuron activity is essential for the coordination of physiological improvements from exercise training.



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**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.09/Y13

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Grant DK138131

**Title:** A simple action reduces high fat diet intake and obesity in mice

**Authors:** \*M. R. BARRETT<sup>1</sup>, L. FANG<sup>2</sup>, J. CZARNY<sup>4</sup>, J. G. WANG<sup>5</sup>, J. M. THOMPSON<sup>3</sup>, M. CREED<sup>6</sup>, A. V. KRAVITZ<sup>7</sup>;

<sup>1</sup>Psychiatry, Washington Univ. St. Louis, Saint Louis, MO; <sup>2</sup>Anesthesiol., Washington Univ. in St Louis, Saint Louis, MO; <sup>3</sup>Washington Univ. in St Louis, SAINT LOUIS, MO; <sup>4</sup>Washington Univ. in STL, Saint Louis, MO; <sup>5</sup>Psychiatry, <sup>6</sup>Washington Univ. in St. Louis, St. Louis, MO; <sup>7</sup>Washington Univ. In St Louis, Saint Louis, MO

**Abstract:** Diets that are high in fat cause overeating and weight gain in multiple species of animals, suggesting that high dietary fat is sufficient to cause obesity. However, high-fat diets are typically provided freely to animals in obesity experiments, so it remains unclear if high-fat diets would still cause obesity if these diets required more effort to obtain. We hypothesized that unrestricted access to high-fat diets is important for these diets to induce overeating, and that requiring mice to perform small amounts of work to obtain high-fat diet would reduce calorie intake and associated weight gain. To test this hypothesis, we developed a novel home-cage based feeding device that either provided high-fat diet in two conditions: either freely, or after mice poked their noses into a port one time - a simple action that is easy for them to do. Consistent with our hypothesis, requiring mice to nose-poke reduced high-fat diet intake and nearly completely prevented weight gain. Requiring mice to nose-poke also reduced low-fat grain-based pellet intake, confirming that this is a general mechanism governing food choice, and not something specific to high-fat diet. We conclude that unrestricted access to food promotes overeating, and that requiring a simple action such as a nose-poke can reduce overeating and weight gain in mice. Our results may have implications for why overeating and obesity are common in modern food environments, which are often characterized by easy access to low-cost unhealthy foods.

**Disclosures:** M.R. Barrett: None. L. Fang: None. J. Czarny: None. J.G. Wang: None. J.M. Thompson: None. M. Creed: None. A.V. Kravitz: None.

**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.10/Y14

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** HHMI Gilliam Fellowship GT15879  
NIH R01HD094809  
UMN MIDB Trainee Seed Grant

**Title:** Mitochondrial dysregulation due to iron deficiency: a potential determinant of hippocampal neuron development

**Authors:** D. C.-S. MENDEZ<sup>1</sup>, L. CARLSON<sup>1</sup>, S. ALI<sup>1</sup>, T. CHRISTENSEN<sup>2</sup>, J. SALISBURY<sup>2</sup>, M. GEORGIEFF<sup>1</sup>, \*T. W. BASTIAN<sup>1</sup>;

<sup>1</sup>Pediatrics, Univ. of Minnesota, Minneapolis, MN; <sup>2</sup>Mayo Clin., Rochester, MN

**Abstract:** Iron deficiency (ID) is the most common micronutrient deficiency in the world causing deficits in neurobehavioral outcomes (e.g., hippocampal-mediated learning and memory) when acquired in early life (fetal through toddler stages). These deficits persist into adulthood despite prompt iron repletion. Human neonatal brain development is metabolically demanding, consuming 60% of the body's oxygen and iron is necessary for mitochondrial enzymes involved in cellular energy (i.e., ATP) production through oxidative phosphorylation (OXPHOS). Thus, early-life ID blunts energy demanding neurodevelopmental processes (e.g., hippocampal neuron dendritic growth/branching) and impairs long-term learning/memory behavior in both dietary iron deficiency anemia and transgenic mouse models of hippocampal neuron-specific ID. This means early-life neuronal iron loss, and not systemic ID or anemia, is responsible. We hypothesized that hippocampal mitochondria in a transgenic dominant negative-transferrin receptor 1 (DNTfR1) mouse model of hippocampal neuron ID would have impaired respiratory capacity and ultrastructure during rapid hippocampal development at postnatal day 21 (p21) and mature adult stage. Unexpectedly, mitochondrial respiratory capacity at p21 showed no significant difference across respiration states between wild-type (WT) (n=8) and DNTfR1 (n=7). Isolated hippocampal mitochondria from 33-42-week-old WT (n=5) and DNTfR1 (n=3) mice showed a significant ID-induced decrease in oxygen consumption rate for ADP to ATP conversion (p=0.0159), and maximal respiration (p=0.0266) with a trending decrease in basal respiration (p=0.0584). The respiratory control ratio, a mitochondrial coupling measure, was spared. To understand potential structural effects of fetal-neonatal ID on long-term mitochondrial and neuronal functional capacity, we used serial block face-scanning electron microscopy. Comparisons between 37-week-old WT (n=3) and DNTfR1 (n=3) suggest a 14% increase in mitochondrial number in the CA1 stratum radiatum of the ID hippocampus (p=0.0279). Furthermore, 3D reconstruction of pyramidal neuron dendrites in WT and DNTfR1 (n= 2 mice; 1 dendrite per mouse) revealed a 20% reduction in spine density (spines/μm) in DNTfR1 CA1 stratum radiatum. Our data shows chronic neuronal ID impairs mitochondrial respiratory capacity and synaptic structure while increasing mitochondrial density in the hippocampus signifying a potential compensatory response. Altogether, the data supports that mitochondrial

dysregulation due to chronic ID can be a potential mechanistic driver of long-term neurodevelopmental and behavior deficits.

**Disclosures:** D.C. Mendez: None. L. Carlson: None. S. Ali: None. T. Christensen: None. J. Salisbury: None. M. Georgieff: None. T.W. Bastian: None.

**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.11/Y15

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Title:** Postdoc associate

**Authors:** Y. XU, \*J. CHENG;  
Baylor Col. of Med., Houston, TX

**Abstract:** Genetic factors play a significant role in obesity susceptibility, with genome-wide association studies (GWAS) and rare variant analyses identifying key genes involved in energy homeostasis. Among these, a rare missense variant (S297R) in the X-linked gene Gpr101 was recently discovered in children with severe early-onset obesity through the Genetics of Obesity Study (GOOS). To explore its functional relevance, we generated Gpr101 S297R knock-in mice using CRISPR-Cas9. Male knock-in mice showed increased susceptibility to high-fat diet (HFD)-induced obesity, characterized by elevated body weight, fat mass, and food intake. Despite hyperleptinemia, they displayed impaired responses to exogenous leptin, suggesting central leptin resistance. Interestingly, these mice also exhibited increased energy expenditure, indicating altered hypothalamic regulation or compensatory thermogenic mechanisms. Our study identifies Gpr101 as a novel regulator of leptin signaling in energy balance and demonstrates how a patient-derived point mutation contributes to body weight gain. The knock-in model serves as a valuable tool for dissecting the underlying mechanisms and offers a platform for testing targeted therapies, emphasizing the importance of translating genetic findings into functional models for therapeutic development.

**Disclosures:** Y. Xu: None. J. Cheng: None.

**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.12/Y16

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

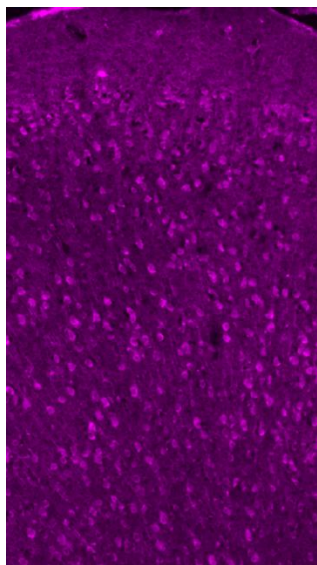
**Support:** NIH Grant RM1NS138808 (S.J.P)

**Title:** Characterization of the transcobalamin receptor (CD320) in the mouse nervous system

**Authors:** \*A. I. ASECOR<sup>1,2,3</sup>, S. J. PLEASURE<sup>1,2,3</sup>;

<sup>1</sup>Neurol., <sup>2</sup>Weill Inst. for Neurosciences, <sup>3</sup>Neurosci. Grad. Program, Univ. of California, San Francisco, San Francisco, CA

**Abstract:** Vitamin B12 (cobalamin) is one of the thirteen essential vitamins and is critical for healthy neurologic function. Severe vitamin B12 deficiency in the central nervous system (CNS) can present with balance, speech, and memory impairments, psychotic episodes, and even dementia-like symptoms in the elderly. The transcobalamin receptor (CD320) is chiefly responsible for the transport of vitamin B12 and is known to be highly expressed on the endothelial cells of the blood-brain barrier. This expression pattern is key to facilitating the transport of vitamin B12 into the CNS. Our research group has published a translational study identifying a novel CD320 autoantibody in patients, who exhibited vitamin B12 deficiency exclusively in the CNS (Pluvinau et al., 2024). These clinical descriptions of both vitamin B12 deficiency and CD320 autoimmunity suggest a role for vitamin B12 and CD320 in sustaining the health, maintenance, and function of the nervous system. Even though it is well documented that vitamin B12 is crucial for neurologic health, CD320 itself has not yet been characterized in the context of the nervous system. Here, we report the first characterization of CD320 expression in both the mouse central and peripheral nervous systems. Immunohistochemistry of mouse neurologic tissue for CD320 shows robust expressions in neurons as well as glia throughout the brain, spinal cord, and peripheral ganglia. The widespread expression of CD320 across the central and peripheral nervous systems suggests significant ramifications of CD320 loss of function to neurons and glial cells, as well as underscores the need to further investigate its contributions to neurologic health. (Image: Immunohistochemistry of CD320 (magenta) on neurons throughout a sample region of the mouse cortex.)



**Disclosures:** A.I. Asencor: None. S.J. Pleasure: None.

## **Poster**

### **PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.13/Web Only

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Grant NS117686  
NSF CAREER 1943514

**Title:** Role of mitochondrial calcium uniporter in neuronal bioenergetics

**Authors:** S. CHOWDHRY, S. SWAIN, R. BOYD, C. LE, D. ROBERTS, \*R. B. RENDEN;  
Physiol. and Cell Biol., Univ. of Nevada, Reno, Reno, NV

**Abstract:** To ensure an energetic supply for the immense energy demand in the brain, neurons efficiently complete the oxidation of glucose via glycolysis and mitochondrial oxidative respiration to maintain synaptic ATP levels, with a heavy reliance on oxidative phosphorylation (OXPHOS) in vivo. Calcium plays a vital role as a secondary messenger regulating neuronal bioenergetics. Mitochondrial calcium uniporter (MCU) is a selective channel responsible for mitochondrial calcium uptake from the cytosol. Despite multiple investigations, the MCU's role in neuronal bioenergetics remains enigmatic. In vivo studies are challenging due to neuronal complexity, making the need for bioenergetically accurate in vitro neuronal models. However, standard culture systems use 25 mM glucose, which is far above physiological brain levels (1-3 mM) and potentially distorts metabolic insights. Our previous work established a model using low glucose (LG, 5 mM), revealing that neurons in “standard” high glucose media rely more on glycolysis, while the LG condition supports a more physiological balance with oxidative phosphorylation. These findings lead us to re-examine the role of the MCU in neuronal mitochondrial respiration, using this in vitro platform. MCU-KO neurons cultured in low-glucose conditions displayed significant morphological and bioenergetic alterations compared to controls. MCU-KO cells exhibited fewer branches and reduced total branch length, accompanied by a lower excitatory-to-inhibitory puncta ratio driven by an increase in inhibitory puncta. Mitochondrial morphology analysis revealed an increase in total mitochondrial area in MCU-KO neuronal neurites, due to increased individual mitochondrion size despite a similar number of mitochondria per 100  $\mu$ m of neurite. Metabolically, Seahorse XF analysis demonstrated that MCU-KO neurons had diminished OXPHOS, whereas basal glycolysis and glycolytic capacity were maintained. ATP measurements further revealed that ATP levels decreased under oxidative-phosphorylation-only conditions but increased under glycolysis-only conditions in MCU-KO neurons relative to controls. Furthermore, while control neurons increased mitochondrial respiration in response to  $\alpha$ -pompilidotoxin (blocking Na-channel desensitization) to augment neuronal workload, MCU-KO neurons showed no change in oxidative phosphorylation, suggesting MCU is required for upregulating mitochondrial ATP production in response to increased demand. Our findings reveal that MCU participates in regulation of mitochondrial respiration in neurons under both basal and stimulated conditions.

**Disclosures:** S. Chowdhry: None. R.B. Renden: None.

**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.14/Z1

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH grants R01ES035851  
NIH grants R21NS133944

**Title:** Selenoprotein I in brain is critical for growth and energy metabolism

**Authors:** \*C. MA<sup>1</sup>, L. NUNES<sup>2</sup>, D. TORRES<sup>4</sup>, F. HOFFMANN<sup>3</sup>, P. HOFFMANN<sup>3</sup>, M. W. PITTS<sup>3</sup>;

<sup>1</sup>Cell and Mol. Biol., <sup>2</sup>Anatomy, Biochemistry, and Physiol., <sup>3</sup>Dept. of Cell and Mol. Biol., Univ. of Hawaii, Honolulu, HI; <sup>4</sup>Pacific Biosci. Res. Ctr., Univ. of Hawai'i at Manoa, Honolulu, HI

**Abstract:** Selenoprotein I (SELENOI) is a phosphotransferase that catalyzes the transfer of the ethanolamine phosphate group from CDP-ethanolamine to lipid donors, generating ethanolamine phospholipids. In humans, rare loss-of-function mutations in SELENOI disproportionately affect plasmalogen-PE content and lead to a form of hereditary spastic paraplegia characterized by lower limb spasticity, ataxia, hypomyelination, cognitive deficits, and impaired growth. To investigate the special role of SELENOI in the central nervous system (CNS), we recently developed a unique CNS-specific SELENOI knockout (KO) mouse model by breeding *Tubal1-Cre* mice with *Seleno1*<sup>fl/fl</sup> mice. These mice exhibited striking behavioral deficits that parallel the neurological symptoms observed in human patients, along with significant hypomyelination in the brain regions involved in motor control. Beyond these neurological changes, the KO mice also display significantly reduced body weight. To further evaluate their metabolic phenotype, we utilized a Bio-Plex Pro™ Mouse Assay to measure levels of Ghrelin, GIP, GLP-1, PAI-1, Glucagon, Insulin, Leptin, and Resistin in serum. Additionally, we used a metabolic measurement system to assess oxygen consumption and CO<sub>2</sub> production, energy expenditure and food intake during both light and dark cycles. Our results indicate that CNS-specific SELENOI KO mice exhibited decreased circulating leptin and increased Ghrelin levels. They also showed elevated energy expenditure, with higher oxygen consumption and CO<sub>2</sub> production compared to control mice. Meanwhile, KO mice display reduced food intake during the dark cycle, their active feeding period. These findings suggest that SELENOI in the CNS plays a critical role in regulating energy homeostasis and food intake. Moving forward, we aim to further explore the hypothalamic mechanisms underlying these metabolic alterations in our conditional KO model.

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

**Poster**

**PSTR231: Energy Metabolism****Location:** SDCC Halls B-H**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM**Program #/Poster #:** PSTR231.15/Z2**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis**Support:** NIH Grant R01NS134958 to SL**Title:** Copper Homeostasis in Noradrenergic Neurons is Required for Normal Thermogenesis**Authors:** \*S. ROY<sup>1</sup>, Y. WANG<sup>1</sup>, A. WADE<sup>1</sup>, K. KIM<sup>2</sup>, A. MUCHENDITSI<sup>1</sup>, A. KRALLI<sup>3</sup>, S. LUTSENKO<sup>1</sup>;<sup>1</sup>Physiol., JOHNS HOPKINS UNIVERSITY, Baltimore, MD; <sup>2</sup>department of Neurol., JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, Baltimore, MD; <sup>3</sup>Physiol., Johns Hopkins Sch. of Med., Baltimore, MD

**Abstract:** In response to cold, noradrenergic neurons release norepinephrine (NE), signaling to brown adipose tissue (BAT) to break down fat for heat production. NE is synthesized by dopamine- $\beta$ -hydroxylase (DBH), which requires copper for catalytic activity. Systemic copper deficiency is associated with low NE levels and hypothermia. However, it is unclear how changes in neuronal copper homeostasis impact NE signaling when systemic copper is normal. To answer this question, we generated mouse strains with copper-transporters Atp7a and Atp7b individually inactivated in DBH-expressing cells. Deletion of Atp7a causes down-regulation of DBH and Atp7b in noradrenergic neurons, thus precluding compensation of the lost Atp7a function. *Atp7a<sup>DBH</sup>* mice show increased food consumption, higher energy expenditure, hypoglycemia, low expression of Ucp1 and Pgc1 $\alpha$ , and lipid accumulation in BAT, along with marked hypothermia, indicating disrupted NE signaling. *Atp7b<sup>DBH</sup>* mice retain ATP7A and DBH expression and do not show significant phenotypic changes except lipid accumulation in BAT and cold sensitivity. Proteomic analysis of micro-dissected locus coeruleus of *Atp7a<sup>DBH</sup>* and *Atp7b<sup>DBH</sup>* mice revealed distinct, non-overlapping changes in the proteome, highlighting non-redundant roles of Atp7a and Atp7b in regulating neuronal metabolism and NE signaling. Together, the results revealed exquisite sensitivity of body thermogenesis to the copper status of noradrenergic neurons.

**Disclosures:** S. Roy: None. Y. Wang: None. A. Wade: None. K. Kim: None. A. Muchenditsi: None. A. Kralli: None. S. Lutsenko: None.

**Poster****PSTR231: Energy Metabolism****Location:** SDCC Halls B-H**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM**Program #/Poster #:** PSTR231.16/Z3

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** Private Donations

**Title:** Gaussian or Hamiltonian: Is a cortical neural network a statistical or a thermodynamical system?

**Authors:** \*E. A. STOLL;  
Western Inst. for Advanced Study, Denver, CO

**Abstract:** Cortical neurons actively maintain a 'cortical up-state', hovering near action potential threshold and allowing stochastic events to drive signaling outcomes. This process of noisy computation results in statistically random firing patterns, which can be modelled with Bayesian statistics (Beck et al. 2008), random connectivity models (Maoz et al. 2020), fanofactor analysis of inter-spike variability (Fayaz et al. 2022), or by modifying the Hodgkin-Huxley equations to account for random electrical noise (Rowat 2007, Austin 2008). Notably, the most reliable models of cortical neurons are composed of stochastic differential equations, which provide an analog membrane potential based on ion channel opening probability, and lead to spiking upon threshold activation (Montbrió & Pazó 2020). This general approach may describe 'noise' at the synapse as a Ornstein-Uhlenbeck process (Goldman et al. 2021) often by applying the Fokker-Planck equations (Ostojic 2011). The question raised by all of these probabilistic models is whether the brain is a statistical system or a thermodynamical system. This problem is highlighted in two recent papers: Tatsukawa & Taramae *P N A S* 2025 (TT) and Stoll *Applied Math* 2024 (S). Both of these approaches describe a computational process of 'differential correlation', with the neural network solving a singular problem: how to be efficient, by not redundantly encoding correlations within a high-dimensional probability density. However, TT make a 'small-noise assumption', while S permits the system to be noisy. Both approaches show that introducing 'an energetic cost' ensures optimality of neural coding with the critical power law. To do so, TT arbitrarily limits the number of available encoder neurons, while S limits the amount of energy entering the system with the empirically-validated quantity of 20W. Both approaches describe the system probabilistically. To do so, TT use a Gaussian (a classical formalism) to describe the distribution of possible system states, while S uses a Hamiltonian (a quantum formalism) to describe the entropy of the system. A comparison of the approaches and their testable predictions is discussed.

**Disclosures:** E.A. Stoll: None.

**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.17/Z4

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis



**Support:** AACR 20-20-26-BORN  
DoD W81XWH2210045

**Title:** Synthetic torpor for anti-cancer therapy

**Authors:** \*A. BATTISON<sup>1</sup>, A. GOMEZ<sup>1</sup>, Y. WU<sup>2</sup>, J. C. BORNIGER<sup>3</sup>;  
<sup>2</sup>Neurosci. and cancer, <sup>3</sup>Neuroscience/Cancer Ctr., <sup>1</sup>Cold Spring Harbor Lab., Cold Spring Harbor, NY

**Abstract:** Mammalian torpor is a controlled hypometabolic state characterized by marked reductions in metabolic rate, core body temperature, and locomotor activity, enabling energy conservation during periods of environmental stress such as cold or food scarcity. Torpor is naturally observed across a range of heterotherms and can also be induced in laboratory mice through food scarcity and cold exposure. Previous work has identified the group of QRFP neurons (“Q neurons”) within the preoptic area of the hypothalamus which can induce a torpor-like state when stimulated. Given the hypermetabolic demand of cancer cells we sought to investigate if torpor/hibernation benefits cancer-related outcomes. We found that DREADD-mediated stimulation of Q neurons stifled the growth of orthotopic EO771 breast tumors as well as reduced the metastatic burden of lewis-lung carcinoma (LLC) cells, suggesting a decreased metabolic state improves cancer-related outcomes. To understand systemic changes that occur due to both the hypometabolic and tumor-state within the body, we performed untargeted metabolomics analysis on the tumor, visceral organs, and plasma samples from torpor and non-torpor animals, as well as tumor or non-tumor bearing controls. Current experiments also seek to understand if a hypometabolic state improves the therapeutic effect of chemotherapy on tumor growth, while also decreasing the toxicity of chemotherapeutic agents on healthy tissue. In summary, we show that the hypometabolic state induced by activation of Q-neurons impacts tumor volume which is complimented by a changing metabolomic landscape in the animal.

**Disclosures:** A. Battison: None. A. Gomez: None. Y. Wu: None. J.C. Borniger: None.

**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.18/Z5

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** FAER MRTG PI GOODNOUGH  
R35GM119522

**Title:** Aldh2\*2 variant delays anesthetic arousal and disrupts neural metabolism in a murine model

**Authors:** \*C. GOODNOUGH<sup>1</sup>, R. HELL<sup>2</sup>, E. GROSS<sup>1</sup>;  
<sup>1</sup>Stanford Univ., Stanford, CA; <sup>2</sup>Stanford Univ., Palo Alto, CA

**Abstract:** Introduction: Impaired anesthetic arousal after surgery can lead to delayed emergence and postoperative delirium. Delayed emergence is marked by prolonged sedation and lack of response to stimuli. Aldehyde metabolism is an understudied research area in anesthetic arousal. Aldehydes, products of lipid peroxidation, disrupt synaptic function, promote neuronal apoptosis and induce inflammation. Aldehyde dehydrogenase 2 (ALDH2) is the key enzyme that metabolized aldehydes. A common genetic variant (ALDH2\*2), affecting nearly 540 million people worldwide, reduces enzymatic activity and impairs detoxification of aldehydes. We hypothesized that ALDH2\*2 impacts arousal from anesthesia by disrupting neural metabolism. Methods: Adult male and female wild-type ALDH2 and ALDH2\*2 knock-in mice (n=8/group) underwent anesthesia by intraperitoneal injection of propofol (200 mg/kg). Before and after anesthesia, open field activity was analyzed by a blinded observer. Arousal was assessed by the righting reflex, grooming behavior in response to 5% sucrose spray, and novel arm entries in a Y-maze. Untargeted metabolomic profiling (LC-MS) was performed on brain, liver, and serum samples at baseline, during anesthesia, and 30 minutes after emergence. Two-way ANOVA with Bonferroni correction was used for statistical comparisons ( $p < 0.05$ ). Results: The return of the righting reflex between wild-type ALDH2 and ALDH2\*2 was not significantly different (WT  $58 \pm 10$  vs ALDH2\*2  $76 \pm 16$  min). However, there was a significant decrease in open field activity normalized to baseline in ALDH2\*2 compared to wild-type (ALDH2\*2  $26 \pm 4\%$  vs WT  $53 \pm 7\%$ ;  $p < 0.05$ ). There was a decrease in grooming time (ALDH2\*2  $5 \pm 5$  vs. WT  $221 \pm 94$  sec;  $p < 0.01$ ) and novel arm entries after anesthesia in ALDH2\*2 mice. Metabolomic analysis revealed distinct biochemical signatures both at baseline and after anesthesia in ALDH2\*2 versus wild-type mice. Most prominently was sphingolipid accumulation during anesthesia in ALDH2\*2 mice, as well as elevated glutathione levels and disruption of tricarboxylic acid cycle (TCA) intermediates. Conclusion: The ALDH2\*2 variant impairs behavioral arousal from propofol-induced anesthesia. The observed deficits in grooming and exploratory activity, along with metabolomic alterations, particularly sphingolipid accumulation and TCA cycle disruption, highlight a potential role for aldehyde-mediated metabolic dysfunction in anesthetic arousal. These results implicate ALDH2 as a modulator of anesthetic recovery and support further investigation into aldehyde metabolism as a therapeutic target for perioperative neurocognitive vulnerability.

**Disclosures:** C. Goodnough: None. R. Hell: None. E. Gross: None.

## **Poster**

### **PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.19/Z6

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Title:** Hormesis and neuroplasticity: metabolic adaptations in the hippocampus induced by running exercise.

**Authors:** \*A. P. VAZQUEZ<sup>1</sup>, B. BELLO<sup>2</sup>, S. RODRIGUEZ<sup>3</sup>, K. MARIN HERNANDEZ<sup>4</sup>, D. RIVERA<sup>5</sup>, D. RUIZ<sup>6</sup>, F. VIZCARRONDO<sup>7</sup>, N. CHORNA<sup>8,9</sup>;

<sup>1</sup>Univ. of Puerto Rico Sch. of Med., San Juan, Puerto Rico; <sup>2</sup>Celular Mol. Biol., Univ. of Puerto Rico Rio Piedras Campus, San Juan, PR; <sup>3</sup>Chem., <sup>4</sup>Celular Mol. Biol., <sup>5</sup>Interdisciplinary, Univ. of Puerto Rico Rio Piedras Campus, San Juan, Puerto Rico; <sup>6</sup>Interdisciplinary, Univ. of Puerto Rico Rio Piedras Campus, San Juan, PR; <sup>7</sup>Cell. Mol. Biol., Univ. of Puerto Rico Rio Piedras Campus, San Juan, Puerto Rico; <sup>8</sup>Biochem., Univ. of Puerto Rico Med. Sch., San Juan, Puerto Rico; <sup>9</sup>Biochem., Univ. of Puerto Rico Med. Sch., San Juan, PR

**Abstract:** Low-level environmental stressors, including health-enhancing challenges such as voluntary running exercise, intermittent fasting, and cognitive stimulation, promote neuronal resilience—a phenomenon known as hormesis. In hormesis, mild stressors elicit adaptive responses that enhance function, while higher doses may have harmful effects. This concept provides a framework for understanding how running-induced metabolic adaptations in the hippocampus support neurogenesis and memory enhancement. However, the metabolic mechanisms underlying these effects remain unclear. This study examines how running-induced hippocampal metabolic changes align with hormesis, potentially promoting cognitive improvement. Here, we investigate the metabolic adaptations in the hippocampus triggered by running exercise that underpin hormesis-based neuroplasticity. Male C57BL/6J mice (20 weeks old) were randomly assigned to sedentary (SED) or running (RUN) groups, with the RUN group engaging in 8 weeks of voluntary exercise. Hippocampal metabolites were analyzed using gas chromatography/mass spectrometry and liquid chromatography/mass spectrometry, followed by Univariate, Chemometric, and Enrichment analyses. To assess cognitive function, mice completed the Barnes maze, evaluating spatial navigation and problem-solving abilities. Running significantly altered neurotransmitter levels, decreasing glutamic acid and aspartic acid while increasing serotonin and glutamine. GABA levels remained stable, maintaining neurochemical balance. The RUN group demonstrated improved performance in the Barnes maze, indicating enhanced cognitive function likely linked to the observed metabolic adaptations. The reduction in excitatory neurotransmitters glutamic acid and aspartic acid aligns with hormesis, suggesting that running, as a mild metabolic stressor, reduces excitotoxicity while promoting neural adaptation. The concurrent increase in serotonin may further enhance cognitive resilience by balancing excitatory activity. These findings demonstrate that running-induced hippocampal metabolic changes exemplify hormetic responses, contributing to exercise-induced cognitive improvement.

**Disclosures:** A.P. Vazquez: None. B. Bello: None. S. Rodriguez: None. K. Marin Hernandez: None. D. Rivera: None. D. Ruiz: None. F. Vizcarrondo: None.

## **Poster**

### **PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.20/Z7

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** JSPS KAKENHI 23K24735  
JST FOREST JPMJFR205M

**Title:** Exhaustive Exercise Induces Protein Targeting to Glycogen (PTG) Expression in the Brain: Involvement of Monoamines

**Authors:** \*R. TAKAMIZAWA, D. FUNABASHI, S. DOBASHI, T. MATSUI;  
Univ. of Tsukuba, Tsukuba, Japan

**Abstract:** Glycogen supercompensation occurs earlier in the hippocampus and cortex than in skeletal muscle following exhaustive exercise; however, its neuromolecular mechanisms remain unclear. Unlike in skeletal muscle, the synthesis of brain glycogen localized primarily in astrocytes is regulated in an insulin-independent manner via protein targeting to glycogen (PTG), which is induced by noradrenergic (NA) activity. As NA promotes PTG expression in cultured cortical astrocytes, we hypothesized that exhaustive exercise-induced increases in NA activity elevate PTG expression in the cortex and hippocampus.

To test this hypothesis, we first examined whether exhaustive exercise induces PTG protein expression in the brain. Male C57BL/6J mice were divided into exercise and non-exercise groups and subjected to treadmill running at 25 m/min until exhaustion. Immediately after exercise, mice were euthanized under isoflurane anesthesia, and blood glucose and lactate levels were measured. Soleus and plantaris muscles, as well as brain regions (hippocampus, cortex, hypothalamus, and cerebellum), were collected to assess PTG protein levels. At baseline, PTG protein levels were lowest in the plantaris muscle and highest in the hippocampus. Exhaustive exercise (152 ± 20 min) caused a significant rise in blood lactate and a marked decrease in blood glucose. Under these conditions, PTG protein expression significantly increased only in the hippocampus, and this increase was negatively correlated with blood glucose levels.

Next, we examined whether hippocampal PTG mRNA expression is promoted via monoaminergic activity during exhaustive exercise. Using the same protocol as described above, brain regions (hippocampus, cortex, hypothalamus, and cerebellum) were collected immediately after exercise, and PTG mRNA levels and concentrations of monoamines, including NA, were quantified. The NA metabolite MHPG increased significantly across all examined brain regions, while the dopamine (DA) metabolite DOPAC increased selectively in the hippocampus and hypothalamus. PTG mRNA expression in the cortex increased approximately 1.5-fold in correlation with MHPG levels. In the hippocampus and hypothalamus, PTG mRNA levels were positively associated with both MHPG and DOPAC.

Our findings demonstrate that exhaustive exercise acutely induces PTG protein expression in the hippocampus, potentially contributing early-phase glycogen supercompensation. Moreover, hippocampal PTG gene expression is likely promoted by both NAergic and DAergic activity, suggesting a region-specific mechanism for brain glycogen synthesis following exhaustive exercise.

**Disclosures:** R. Takamizawa: None. D. Funabashi: None. S. Dobashi: None. T. Matsui: None.

**Poster**

**PSTR231: Energy Metabolism**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR231.21/Z8

**Topic:** G.05. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** JST FOREST JPMJFR205M  
JSPS KAKENHI 23K24735

**Title:** Lactate Receptor HCAR1 Activation Induces Exhaustion Independent of Skeletal Muscle Energy Depletion

**Authors:** \*T. MATSUI<sup>1</sup>, D. FUNABASHI<sup>2</sup>, R. TAKAMIZAWA<sup>3</sup>, S. DOBASHI<sup>4</sup>;

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**Abstract:** Unlike skeletal muscle, brain ATP levels remain stable during exhaustive exercise, suggesting the presence of a neuroprotective mechanism. However, the neuromolecular basis of this mechanism remains unknown. During exhaustive exercise, lactate levels rise markedly in both the blood and brain, serving not only as an energy substrate via the lactate shuttle but also as a signaling molecule. Since the lactate receptor hydroxycarboxylic acid receptor 1 (HCAR1) mediates inhibitory signaling in neurons, we thus hypothesized that HCAR1 activation accelerates exhaustion independently of skeletal muscle energy depletion. We first examined whether HCAR1 agonism affects time to exhaustion and energy metabolism. Male C57BL/6 mice were divided into two groups and intraperitoneally injected with either vehicle or an HCAR1 agonist. Fifteen minutes post-injection, mice were subjected to treadmill running until exhaustion. Immediately after exhaustion, mice were euthanized under isoflurane anesthesia, and blood glucose and lactate levels were measured. Plantaris muscles were rapidly dissected and subjected to metabolomic analysis. While vehicle-treated mice reached exhaustion in approximately 107 minutes and exhibited hypoglycemia, agonist-treated mice ran only one-fifth as long without significant hypoglycemia. Metabolomic profiling revealed that ATP levels in the plantaris muscle, typically reduced at exhaustion, were preserved in the agonist group, along with upstream (glucose-1-phosphate) and downstream (inosine) metabolites. Next, we assessed whether HCAR1 activation induces fatigue-like running behavior. Using the same protocol, mice were placed on the treadmill for 15 minutes before starting the exhaustion trial. Behavior was recorded from above, and positional distribution (front, middle, rear, and shock zone) was quantified at three time points: pre-exercise, the first 5 minutes of running, and the final 5 minutes before exhaustion. HCAR1 activation significantly reduced both pre-exercise activity and total running time, while preventing exercise-induced hypoglycemia. Vehicle-treated mice exhibited a progressive rearward shift, primarily during the final phase of exercise, whereas agonist-treated mice exhibited significantly increased time spent in the rear and shock zones within the first 5 minutes of running. Our findings demonstrate that systemic HCAR1 activation accelerates exhaustion during endurance exercise independent of peripheral energy depletion. Circulating lactate, which increases during exercise, likely acts as a central fatigue factor via HCAR1-mediated inhibitory signaling in the brain.

**Disclosures:** T. Matsui: None. D. Funabashi: None. R. Takamizawa: None. S. Dobashi: None.

**Poster**

**PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.01/Z9

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** JSPS Grant19J22270  
JSPS Grant19J22270  
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JSPS Grant 23K19399

**Title:** Cross-correlation analysis of orexin neuron activity and EEG components in orexin-intact and orexin-ko mice: additional investigation into “deficiency of orexin signaling during sleep is involved in abnormal rem-sleep architecture in narcolepsy”

**Authors:** \*H. ITO<sup>1,2</sup>, N. FUKATSU<sup>3</sup>, A. YAMANAKA<sup>4</sup>;  
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**Abstract: Background**

Narcolepsy, produced by deficient orexin signaling, features cataplexy and frequent transitions to REM sleep, yet the neuronal mechanisms underlying these REM-sleep-related abnormalities were unclear. We previously found that the activity dynamics of orexin neurons during NREM and REM sleep regulate REM sleep architecture and the loss of this function contributes to the abnormal REM sleep architecture in narcolepsy (Ito et al., *PNAS* 2023). Intermittent synchronous activity during NREM sleep regulates transition to REM sleep, whereas activity by subpopulation during REM sleep restrains later REM accumulation and cataplexy. Orexin neurons that lacked orexin peptides were less active during REM sleep and were mostly silent during cataplexy. However, in that report, temporal relationship between orexin neuron activity during NREM sleep and EEG components—and the role of orexin peptides in this relationship—has not been carefully investigated.

**Objective**

Characterize the temporal relationship between orexin-neuron activity and band-limited EEG power during NREM sleep, and determine how loss of orexin peptides alters this coupling.

**Methods**

GCaMP6s fiber photometry (24 h) was combined with EEG/EMG recording in orexin-tTA (peptide intact, n = 6) and prepro orexin KO orexin-Flp KI/KI (peptide KO, n = 5) mice. During NREM sleep, EEG power for  $\delta$  (1-4 Hz),  $\theta$  (6-10 Hz),  $\alpha$  (11-14 Hz) and  $\beta$  (15-20 Hz) bands was cross-correlated ( $\pm 150$  ms, 1 ms bins) with z-scored  $\Delta F/F$  and averaged per animal.

## Results

In orexin peptide intact mice, orexin neuron activity was tightly coupled to fast EEG component power drops:

- $\theta/\alpha/\beta$  Peak  $r = -0.206 \pm 0.007$ ,  $-0.260 \pm 0.012$ ,  $-0.274 \pm 0.013$  at lags of  $+5.8 \pm 2.6$  ms,  $-1.0 \pm 2.8$  ms,  $-6.0 \pm 3.1$  ms, respectively.
- $\delta$  power increased modestly ( $+0.045 \pm 0.025$ ) at  $-30.5 \pm 9.9$  ms.

In orexin peptide KO mice, the same fast-component coupling was both weaker and delayed:

- $\theta/\alpha/\beta$  Peak  $r = -0.151 \pm 0.038$ ,  $-0.153 \pm 0.035$ ,  $-0.148 \pm 0.032$  at  $+9.6 \pm 0.6$  ms,  $+3.8 \pm 1.2$  ms,  $+1.7 \pm 2.7$  ms, respectively
- $\delta$  coupling fell to  $+0.030 \pm 0.017$  and shifted to  $+23 \pm 125$  ms.

$\theta$ ,  $\alpha$ , and  $\beta$  power were reduced by 27 %, 41 %, and 46 %, respectively, compared with orexin peptide-intact mice;  $\alpha$  and  $\beta$  significant,  $p = 0.035$ ,  $0.019$ .  $\beta$  lag flipped from  $-6.0$  ms (orexin leading) to  $+1.7$  ms (EEG leading;  $p = 0.028$ ).

## Conclusion

During NREM sleep, orexin neuron activity in orexin peptide intact mice correlates sharply with suppression of fast EEG components. In orexin peptide KO mice, these changes are reduced, and their peak lags shift by  $+4$ - $8$  ms, and the  $\beta$  band reverses from orexin-leading to EEG-leading. Thus, the loss of orexin peptides may weaken and delay fast EEG component coupling.

**Disclosures:** H. Ito: None. N. Fukatsu: None. A. Yamanaka: None.

## Poster

### PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.02/Z10

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** NIH R01 NS098813  
NIH R01 NS136808

**Title:** Chemogenetic activation of lateral hypothalamic CaMKII $\alpha$  neurons as hypocretin/orexin neurons degenerate in Orexin-tTA; TetO-DTA mice

**Authors:** \*C. YIN<sup>1,2</sup>, S. LEE<sup>2</sup>, Y. SUN<sup>2</sup>, T. S. KILDUFF<sup>2</sup>;  
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**Abstract:** Degeneration of the hypothalamic hypocretin/orexin (Hcrt) neurons underlies the sleep disorder Narcolepsy Type 1 (NT1), leading to excessive daytime sleepiness (EDS), cataplexy and other sleep disturbances. The lateral hypothalamus (LH) plays a critical role in sleep-wake regulation. We recently showed that LH CaMKII $\alpha$  neurons are wake-active and that chemogenetic activation of these cells prolongs wakefulness for as long as 6 hours (Heiss et al., 2024, PNAS). We hypothesized that LH CaMKII $\alpha$  neuron activation might compensate for the loss or dysfunction of Hcrt neurons and counteract EDS in narcolepsy, thereby serving as a

potential therapy for individuals suffering from hypoarousal disorders. *Orexin-tTA; TetO-DTA* mice (n = 8) mice were bilaterally injected with AAV2-CaMKII $\alpha$ -hM3D(Gq)-mCherry into the LH and implanted with telemetry transmitters for EEG/EMG recording. Hcrt neurons were ablated by substituting doxycycline-containing chow with normal rodent chow (Dox (-) condition) for 6 weeks. When the Hcrt neurons were either partially-degenerated (3 weeks Dox (-)) or fully degenerated (6 weeks Dox (-)), LH CaMKII $\alpha$  neurons were chemogenetically activated by injection of deschloroclozapine (DCZ, 0.3mg/kg, i.p.) at ZT18. As a control, each mouse also received a saline injection a day before. Activation of LH CaMKII $\alpha$  neurons profoundly increased Wakefulness and reduced NREM sleep in both partially (Wakefulness:  $p < 0.001$ ; NREM:  $p < 0.001$ ) and fully (Wakefulness:  $p < 0.001$ ; NREM:  $p < 0.001$ ) Hcrt neuron-degenerated mice. Furthermore, DCZ treatment significantly reduced both the number of cataplexy bouts ( $p = 0.048$ ) and bout duration ( $p = 0.035$ ) in fully Hcrt neuron-degenerated mice but not when partially degenerated for either the number of cataplexy bouts ( $p = 0.196$ ) or bout duration ( $p = 0.055$ ). Our results show that activation of LH CaMKII $\alpha$  neurons has profound wake-promoting effects even in the absence of Hcrt neurons, indicating that the wake-promoting effects of LH CaMKII $\alpha$  neurons are independent of the Hcrt system. Consequently, LH CaMKII $\alpha$  neuron activation may have therapeutic effects on the primary symptoms of narcolepsy: EDS and cataplexy.

**Disclosures:** C. Yin: None. S. Lee: None. Y. Sun: None. T.S. Kilduff: None.

## **Poster**

### **PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.03/Z11

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** R03 NS128993-02

**Title:** The role of neurotensin-expressing neurons of the extended ventrolateral preoptic nucleus in REM sleep regulation

**Authors:** \*I. BOCCALARO<sup>1</sup>, E. RILLOSI<sup>2</sup>, S. NARDONE<sup>3</sup>, P. FULLER<sup>4</sup>, R. DE LUCA<sup>5</sup>, E. ARRIGONI<sup>6</sup>;

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**Abstract:** The ventrolateral preoptic nucleus (VLPO) plays a crucial role in the regulation of both non-rapid eye movement (NREM) and REM sleep, but understanding the underlying circuitry has proven challenging. Research over the past two decades has identified galanin-expressing neurons within the VLPO (VLPO<sup>Gal</sup>) as the key drivers of sleep. These neurons



appear divided into two clusters: the core (cVLPO) and the extended (eVLPO). Lesion and anatomical studies suggest that cVLPO<sup>Gal</sup> neurons regulate NREM sleep, while eVLPO<sup>Gal</sup> neurons are responsible for REM sleep. However, how eVLPO<sup>Gal</sup> neurons drive REM sleep remains unclear due to their proximity to cVLPO and the lack of selective markers. We recently identified neurotensin (Nts) as a specific marker for galanin-expressing neurons in the eVLPO, enabling selective manipulation from the neighboring cVLPO<sup>Gal</sup> neurons. Notably, Nts is not expressed in cVLPO. Using fiber photometry in Nts-Cre mice expressing GCaMP, we found that eVLPO<sup>Nts</sup> neurons exhibit a gradual increase in calcium activity just before NREM-to-REM transitions (n=118 transitions from N=5 mice) and a sharp decline upon awakenings from REM sleep (n=31 REM-to-wake transitions from N=5 mice) and chemogenetic inhibition of eVLPO<sup>Nts</sup> neurons decreases REM sleep (n=17 trials from N=9 mice). Additionally, our conditional anterograde tracing shows that eVLPO<sup>Nts</sup> neurons project to and inhibit areas known to suppress REM sleep, including the ventrolateral periaqueductal gray (vlPAG) and the locus coeruleus (LC). Furthermore, we found that mice exposed to stressors (cage exchange with other male or female bedding) have difficulty entering REMs, suggesting that under stress conditions they prioritize NREM over REM sleep. We propose that the activation of the eVLPO<sup>Nts</sup> neurons could enhance REM sleep both under physiological conditions and restore REM sleep during stress conditions. Our results show that eVLPO<sup>Nts</sup> neurons are active during REM sleep and they are critical for REM initiation, likely by inhibiting GABAergic neurons in the vlPAG and monoaminergic neurons in the LC, thereby disinhibiting pontine REM-generating circuits. Activation of the eVLPO<sup>Nts</sup> neurons could reverse stress-induced REM suppression and potentially promote stress resilience through sleep regulation.

**Disclosures:** I. Boccalaro: None. E. Rilloso: None. S. Nardone: None. P. Fuller: None. R. De Luca: None. E. Arrigoni: None.

## **Poster**

### **PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.04/Z12

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** NIA Grant K99AG086609

**Title:** Homeostatic sleep pressure alters hypocretin neuron activity

**Authors:** \*O. C. GONZALEZ, C. EGEBJERG, J. MORGA-RODRIGUEZ, C. E. LUFF, G. WANG, J. A. KAUER, L. DE LECEA;  
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**Abstract:** Sleep is a universal behavioral state observed across all animals. Its role in learning and memory has been established, and disrupted sleep has been associated with various neurological and psychiatric disorders. As the amount of time spent in wake increases, there is a

buildup of pressure to sleep. Following sleep deprivation, this buildup of sleep pressure leads to homeostatic sleep rebound. How the amount of time spent in wake impacts specific brain circuits, thereby driving it towards sleep, remains to be fully understood. Wake-promoting hypocretin (Hcrt) neurons in the lateral hypothalamus are critical mediators of sleep architecture; therefore, it is likely that their activity is influenced by sleep pressure. In this study we conducted long-term recordings of hypocretin neurons to understand the impact of sleep pressure on their activity. We found that hypocretin neuron activity differed during periods of high (ZT0) and low (ZT12) sleep pressures. We analyzed the GCaMP signal from Hcrt neurons at the sleep-to-wake transition in freely behaving mice using fiber photometry. We found a significantly larger Hcrt GCaMP signal at sleep-to-wake transitions in recordings starting at ZT0, when mice have highest amounts of sleep pressure, as compared to ZT12 recordings, when sleep pressure is lowest. To test whether this phenomenon was driven by changes in intrinsic excitability or synaptic currents of Hcrt neurons, we performed ex vivo whole-cell patch clamp recordings from Hcrt neurons expressing eGFP in acute brain slices collected at ZT0, ZT12. We found that the resting membrane potential of Hcrt neurons sampled at high sleep pressure were depolarized relative to those from the low sleep pressure condition. Additionally, action potential threshold for high sleep pressure Hcrt neurons was reduced. Together, these results suggest elevated intrinsic excitability for Hcrt neurons because of increased sleep pressure. We next explored the possibility that changes in excitatory synaptic inputs onto Hcrt neurons may contribute to the observed differences in photometry data at these time points. We recorded spontaneous excitatory post-synaptic currents (sEPSC) from Hcrt neurons expressing eGFP in acute brain slices collected at ZT0, ZT12. We found that sEPSCs recorded under high sleep pressure (ZT0) were significantly larger than those recorded at low sleep pressure (ZT12). Together, these data provide novel insights into the mechanisms underlying local circuit sleep pressure in wake-promoting Hcrt neurons in the lateral hypothalamus, and their regulation of sleep architecture.

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## **Poster**

### **PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.05/AA1

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** NIH Grant R21NS113589  
NIH Grant R01HL150836  
NIH Grant R01NS136808

**Title:** Global and local deletion of the NOP receptor disrupts both spontaneous and NOP agonist-induced sleep

**Authors:** \*Y. SUN<sup>1</sup>, R. TISDALE<sup>1</sup>, S. LEE<sup>1</sup>, A. OZAWA<sup>2</sup>, C. YIN<sup>1</sup>, G. SCHELDROP<sup>1</sup>, L. TOLL<sup>2</sup>, M. R. BRUCHAS<sup>3</sup>, T. S. KILDUFF<sup>1</sup>;

<sup>1</sup>SRI Intl., Menlo Park, CA; <sup>2</sup>Biomed. Sci., Florida Atlantic Univ., Jupiter, FL; <sup>3</sup>Dept. of Anesthesiol. and Pain Med., Univ. of Washington, Seattle, WA

**Abstract:** Introduction: We have previously shown that NOPR agonism induced sleep and increased EEG delta power in rats, mice and non-human primates, suggesting that the N/OFQ-NOPR system may have an unrecognized role in sleep/wake regulation. In the present studies, we tested the hypothesis that the N/OFQ-NOPR system is a component of the endogenous sleep/wake regulatory system by deleting NOPRs globally. We then determined whether interruption of NOPR transmission specifically in the lateral hypothalamic area (LHA), locus coeruleus (LC) or lateral habenula (LHb) contributed to the effects observed after global NOPR deletion. Methods: Homozygous *NOPR*<sup>lox/lox</sup> mice were bred with B6.Cg-*Ndor1*<sup>Tg(UBCcre/ERT2)1Ejb/1J</sup> mice to produce a strain (iNOPR mice) in which deletion of NOPRs could be induced by tamoxifen (TMX). In the local deletion study, AAV2-CMV-Cre-eGFP or AAV10-CMV-hrGFP was injected into the LHA, LC and LHb of *Oprl1-3*<sup>lox/lox</sup> mice to eliminate *Oprl1* (=NOPR) expression in local brain areas. EEG, EMG, activity and T<sub>b</sub> were measured by telemetry. Results: TMX administration to homozygous Cre<sup>+</sup> iNOPR mice resulted in a massive knockdown of NOPR expression as determined by Western blotting. Whereas administration of the NOPR agonist Ro64-6198 (3 mg/kg, i.p.) suppressed activity, reduced T<sub>b</sub> and increased NREM sleep in Cre<sup>+</sup> iNOPR mice before TMX administration and in Cre<sup>-</sup> mice both before and after TMX administration, these effects were abolished following TMX treatment in the Cre<sup>+</sup> iNOPR mice, providing pharmacological confirmation of NOPR deletion. Within-animal comparisons of pre vs. post TMX-treated Cre<sup>+</sup> iNOPR mice revealed that NOPR deletion produced partial insomnia with 5.3±1.4% more Wake time over 24-h (p = 0.028) and 11.5±1.4% more Wake during the light phase (p < 0.001), the major sleep period in mice. Conversely, NREM sleep decreased by 4.7±1.4% (p = 0.04) over 24-h and 10.4±1.4% (p < 0.001) during the light phase. In the local NOPR deletion studies, as expected, treatment with the NOPR agonist Ro64-6198 (3 mg/kg, i.p.) increased NREM sleep and reduced activity and T<sub>b</sub> in control mice but these changes were completely blocked in LHA NOPR deletion mice. In contrast, the effects of Ro64-6198 were intact in LHb NOPR deletion and NOPR deletion from the LC produced intermediate effects. Conclusion: The global NOPR deletion results support the hypothesis that loss of endogenous NOPR tone reduces sleep amounts and increases wake. NOPRs within the LHA appear to play a role in mediating Ro64-6198 effects on sleep/wake and thermoregulatory physiology whereas NOPRs within the LHb have no such role.

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## Poster

### PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.06/AA2

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** JSPS Grant JP23KJ0266  
University of Tsukuba Ph.D. Program in Humanics Grant

**Title:** Light-dependent regulation of sleep and wakefulness

**Authors:** \*A. IMAMURA<sup>1</sup>, K. MIYATAKE<sup>2</sup>, S. AKAHIRA<sup>2</sup>, A. IHARA<sup>2</sup>, S. HONJOH<sup>2</sup>;  
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**Abstract:** Sleep is a universal and essential physiological process among species with a nervous system. Light has been widely observed to modulate sleep-wake states, promoting sleep in nocturnal species and wakefulness in diurnal species. However, despite its ubiquity, the neural mechanisms by which light controls the timing of sleep and wakefulness remain unclear. To investigate the roles of specific brain regions in sleep-wake regulation, we performed targeted ablations in adult male C57BL/6J mice (P90-120, n = 11 per group) and examined their effects on nocturnal behavior. Using a Cre-dependent taCasp3 AAV approach, we selectively induced apoptosis in the preoptic area (POA) of the hypothalamus while minimizing effects on fibers of passage. Sleep-wake behavior was monitored using EEG/EMG recordings. In wild-type (WT) mice, POA lesions abolished the normal difference in sleep amount between the light and dark phases, suggesting that the POA is essential for regulating nocturnal sleep patterns. Environmental cues entrain circadian rhythms, ensuring that sleep occurs at appropriate times within the 24-hour light-dark cycle. In addition to circadian regulation, light can directly and rapidly influence sleep and wakefulness—a phenomenon known as “masking” (Hubbard et al., 2013). *VGAT-Cre; Bmal flox/flox* mice, which lack circadian rhythmicity under constant darkness but retain masking responses (Weaver et al., 2018), provide a model for studying light effects independent of the circadian clock. To assess whether the POA contributes to the masking effect, we lesioned the POA in *VGAT-Cre; Bmal flox/flox* mice. These mice showed significantly increased wakefulness and reduced sleep during the light phase (two-way ANOVA,  $p < 0.05$ ), while changes during the dark phase were not statistically significant. Consequently, the normal difference in sleep-wake amounts between light and dark phases was abolished, indicating that POA lesions impair masking independently of circadian modulation. Our findings demonstrate that the POA is crucial for mediating light-dependent, circadian-independent control of sleep and wakefulness, and for regulating nocturnal behavior in mice. This study advances our understanding of the neural mechanisms through which environmental light cues influence sleep via specific hypothalamic circuits.

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**Poster**

**PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.07/AA3

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** NIH R01NS118856  
NIH R01NS073613  
NIH R01NS091126

**Title:** Suprachiasmatic Neuromedin-S neurons regulate arousal

**Authors:** \*Y. WU<sup>1,2</sup>, R. DE LUCA<sup>2</sup>, R. BROADHURST<sup>2</sup>, A. VENNER<sup>2</sup>, J. CAMPBELL<sup>3</sup>, E. ARRIGONI<sup>2</sup>, P. M. FULLER<sup>1,2</sup>;

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**Abstract:** Mammalian circadian rhythms, which orchestrate the daily temporal structure of biological processes, including the sleep-wake cycle, are primarily regulated by the circadian clock in the hypothalamic suprachiasmatic nucleus (SCN). The SCN clock is also implicated in providing an arousal 'signal,' particularly during the wake-maintenance zone (WMZ) of our biological day, essential for sustaining normal levels of wakefulness in the presence of mounting sleep pressure. Here we identify a role for SCN Neuromedin-S (SCN<sup>NMS</sup>) neurons in regulating the level of arousal, especially during the WMZ. We used chemogenetic and optogenetic methods to activate SCN<sup>NMS</sup> neurons in vivo, which potently drove wakefulness. Fiber photometry confirmed the wake-active profile of SCN<sup>NM</sup> neurons. Genetically ablating SCN<sup>NMS</sup> neurons disrupted the sleep-wake cycle, reducing wakefulness during the dark period and abolished the circadian rhythm of body temperature. SCN<sup>NMS</sup> neurons target the dorsomedial hypothalamic nucleus (DMH), and photostimulation of their terminals within the DMH rapidly produces arousal from sleep. Pre-synaptic inputs to SCN<sup>NMS</sup> neurons were also identified, including regions known to influence SCN clock regulation. Unexpectedly, we discovered strong input from the preoptic area (POA), which itself receives substantial inhibitory input from the DMH, forming a possible arousal-promoting circuit (SCN->DMH->POA). Finally, we analyzed the transcriptional profile of SCN<sup>NMS</sup> neurons via single-nuclei RNA-Seq, revealing three distinct subtypes. Our findings link molecularly-defined SCN neurons to sleep-wake patterns, body temperature rhythms, and arousal control.

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**Poster**

**PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.08/AA4

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** NHLBI Grant 5R01HL172283-02

**Title:** Population dynamics of lateral hypothalamic neurons in prefrontal cortical regulation of REM sleep

**Authors:** \*J. HONG<sup>1</sup>, Z. YIN<sup>2</sup>, X. JIN<sup>2</sup>, S. CHUNG<sup>1</sup>, F. WEBER<sup>1</sup>;

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**Abstract:** The lateral hypothalamus (LH) orchestrates essential physiological functions and behaviors for survival, including sleep-wake regulation. Previously, we have shown that excitatory projections from the medial prefrontal cortex (mPFC) to the LH promote REM sleep. However, due to the complex heterogeneity and functional diversity, the dynamics in the LH population activity driving brain state transitions and their modulation by prefrontal inputs have remained largely unknown. By combining large-scale in vivo electrophysiological recordings with dimensionality reduction, we found that the LH population activity follows stereotypic trajectories within the neural state space at sleep state transitions. At NREM→REM transitions, the population trajectories crossed a critical point within NREM sleep space, from which they diverged either toward REM sleep or wakefulness. Interestingly, activation of mPFC pyramidal neurons induced transitions to REM sleep only when delivered near this critical point. Activations performed at other locations within the state space influenced the firing rate of individual neurons but failed to trigger REM sleep. Consequently, brain state transitions resulting from mPFC activation depended on the location of LH population activity with the neural state space at laser onset. LH neurons that were activated or inhibited by mPFC activation differed in their correlation with a shared activity component capturing infraslow oscillations during sleep. Collectively, our findings elucidate critical dynamics within the LH population activity at state transitions and reveal mechanisms through which cortical top-down inputs shape LH population dynamics to regulate REM sleep.

**Disclosures:** J. Hong: None. Z. Yin: None. X. Jin: None. S. Chung: None. F. Weber: None.

**Poster**

**PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.09/AA5

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** NIH BRAIN Initiative (U19NS128613)

**Title:** Circadian modulation of noradrenergic activity governs cortical oscillations and sleep quality in mice

**Authors:** F. MASHRUR<sup>1</sup>, C. KJAERBY<sup>4</sup>, V. UNTIET<sup>4</sup>, \*M. NEDERGAARD<sup>2</sup>, M. CETIN<sup>3</sup>;

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**Abstract:** Norepinephrine (NE) released by the locus coeruleus is a critical neuromodulator of sleep-wake regulation and arousal transitions. Recent studies have revealed that NE exhibits infraslow oscillations (~0.02Hz) that organize the microarchitecture of non-rapid eye movement (NREM) sleep. Understanding these dynamics is essential for elucidating the neurochemical basis of sleep quality and developing targeted interventions for sleep disorders. Here, we used high-resolution fiber photometry recordings to monitor NE dynamics in head-fixed mice (n=71) alongside simultaneous cortical electroencephalography (EEG), across multiple sleep-wake cycles. Spectral analysis quantified power in delta (0.5-4 Hz), theta (4-8 Hz), low gamma (30-60 Hz), and high gamma (60-100 Hz) frequency bands. Statistical comparisons were made using paired t-tests and ANOVA. Transitions from NREM to wake were marked by a sharp decrease in delta power and significant increases in low gamma and high gamma power ( $p < 0.01$ ), consistent with phasic NE-driven cortical desynchronization. In contrast, during sustained NREM episodes, NE transients coincided with enhanced delta power and suppressed low gamma activity, with high gamma remaining elevated compared to other bands, indicating a role of NE in shaping intra-NREM spectral architecture. Circadian timing strongly influenced these dynamics: mice-initiated sleep in the early light phase (pre-noon) showed significantly longer NE fluctuation durations compared to post-noon sleepers ( $39.3 \pm 21.1$  vs  $26.72 \pm 15.2$  seconds,  $p < 0.05$ ). These prolonged NE transients correlated with stronger delta power and deeper suppression of low gamma, reflecting improved sleep consolidation. Sustained NE transients during NREM sleep predicted deeper slow-wave activity and improved consolidation metrics, underscoring NE's central role in shaping sleep quality and its potential as a therapeutic target. Together, these findings demonstrate that NE serves both as a rapid switch for sleep-wake transitions and as a fine-tuned modulator of sleep depth and stability. The results refine existing models of neuromodulatory control of sleep by highlighting the circadian gating of NE dynamics and their critical role in determining sleep quality. This has important implications for understanding and treating sleep disruptions in neuropsychiatric and neurodegenerative diseases where noradrenergic signaling is impaired.

**Disclosures:** F. Mashrur: None. C. Kjaerby: None. V. Untiet: None. M. Nedergaard: None. M. Cetin: None.

## **Poster**

### **PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.10/AA6

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** ERDF-Project Brain dynamics, No. CZ.02.01.01/ 00/22\_008/0004643  
Max-Planck Society

**Title:** The locus coeruleus phasic activation prevents the K-complex sleep spindle coupling during NREM sleep

**Authors:** W. GOCH<sup>1</sup>, P. SANDA<sup>1</sup>, \*O. ESCHENKO<sup>2</sup>;

<sup>1</sup>Dept. of Complex Systems, Inst. of Computer Science, Czech Acad. of Sciences, Prague, Czech Republic, Prague, Czech Republic; <sup>2</sup>Max Planck Inst. for Biol. Cybernetics, Tuebingen, Germany

**Abstract:** Slow oscillations (~1Hz), delta waves (1-4Hz), and sleep spindles (10-16Hz), distinct electrophysiological phenomena detected in the EEG during NREM sleep, reflect synchronous discharge of a large population of cortical neurons. The temporal coordination of sleep oscillations with subcortical regions, including the hippocampus, has been implicated in offline memory consolidation (Watts 2012). The Locus Coeruleus (LC) phasic activation during NREM sleep is phase-locked to slow oscillations and sleep spindles; it has also been linked to microarousals, decreased spindle power, and transitions between REM and NREM sleep stages (Kjaerby et al., 2022). Recent findings revealed a correlation between fluctuations in cortical noradrenaline (NE) level and NREM sleep microstructure and transient surges of NE release implicated in the NREM sleep continuity (Osorio-Forero et al., 2021). The K-complex (KC), a singular high-amplitude EEG deflections, is another hallmark EEG feature of NREM sleep. In the presented study, we analyzed the combined EEG and LC recordings in behaving rats to investigate the temporal relationship between the LC-NE neuron firing and KCs. The detection of KCs was established and verified by cortical LFP and unit recordings. The small percentage of KCs cooccurred with LC bursting, which was consistent with previously published results (Eschenko et al., 2012). The waveforms of KCs coupled and uncoupled to the LC burst didn't differ. However, a typical increase in the spindle power up to 1.5 s following a KC was absent in the case of KC-LC coupling. In addition, we explored the impact of the burst-firing of LC-NE neurons on the spectral characteristics of the EEG. We observed differences in the post-KC EEG segments using the Dynamical Time Warping (DTW) combined with conventional clustering methods. The EEG cluster with an overall lower (100uV vs 150uV) amplitude and clear reduction in sigma frequency range (10-15 Hz) was four times more frequently associated with KC-LC coupling than random EEG segments during NREM sleep. These results suggest that phasic NE release might affect the NREM sleep microstructure by overcoming the intracortical and thalamocortical sleep protective mechanisms and trigger the transition towards a lighter sleep or cause a microarousal.

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**Poster**

**PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.11/AA7

**Topic:** G.07. Biological Rhythms and Sleep



**Support:** Harmony Biosciences

**Title:** State-dependent noradrenaline release in the ventrolateral preoptic area of narcoleptic mice

**Authors:** \*E. RILLOSI<sup>1</sup>, R. DE LUCA<sup>2</sup>, B. TOTH<sup>3</sup>, C. BURGESS<sup>4</sup>, T. E. SCAMMELL<sup>2</sup>, E. ARRIGONI<sup>2</sup>;

<sup>1</sup>Neurol., Beth Israel Deaconess Med. Ctr., Boston, MA; <sup>2</sup>Neurol., Beth Israel Deaconess Med. Ctr. - Harvard Med., Boston, MA; <sup>3</sup>Mol. and Behavioral Neurosci. Inst., <sup>4</sup>Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

**Abstract:** Neurons in the ventrolateral preoptic (VLPO) area are essential for initiating and maintaining sleep. During wakefulness, the sleep-promoting VLPO galanin (VLPO<sup>Gal</sup>) neurons are thought to be inhibited by noradrenaline (NA) and other wake-promoting neurotransmitters, and optogenetic stimulation of noradrenergic locus coeruleus terminals in the VLPO triggers arousals from sleep. In this study, we measured changes in NA tone in the VLPO across the sleep-wake cycle of wild-type (WT) and in a mouse model of narcolepsy (orexin<sup>DTR</sup> mice). Orexin<sup>DTR</sup> mice express the human diphtheria toxin receptor (DTR)-EGFP construct targeted to the prepro-orexin locus, and 1 week after diphtheria toxin administration (50 ng/g, intramuscularly, 2 doses), approximately 99% of the orexin neurons are ablated, resulting in a narcolepsy-like phenotype, including cataplexy. We expressed a G-protein-coupled receptor activation-based NA sensor (GRAB<sub>NA</sub>) in the VLPO of WT and orexin<sup>DTR</sup> mice and implanted an optical fiber above the VLPO. We found the GRAB-NA signal in the VLPO is higher during wakefulness than during NREM and REM sleep ( $n = 8$ ), but in orexin<sup>DTR</sup> mice, NA tone in the VLPO was 42% lower during wakefulness than in WT controls ( $n = 8$ ). Furthermore, we found that pitolisant, an H3 receptor antagonist/inverse agonist indicated to treat excessive daytime sleepiness in people with narcolepsy, increased NA levels in VLPO. Specifically, injection of pitolisant (5, 10, and 20 mg/kg i.p.) dose-dependently increased NA levels in the VLPO and increased wakefulness ( $n = 8$ ). These findings indicate that lower NA tone in the VLPO may contribute to the excessive daytime sleepiness of narcolepsy. In addition, pitolisant increases NA levels in the VLPO, and inhibition of sleep-promoting VLPO neurons may contribute to its wake-promoting effects.

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**Poster**

**PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.12/AA8

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** Swiss National Science Foundation 184759 and 214851  
Borbély-Hess Foundation Fellowship

**Title:** Investigating the Activity of Locus Coeruleus Projection Neurons During Sleep Wake States in Mice

**Authors:** \*G. FOUSTOUKOS, A. LUTHI;  
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**Abstract:** The locus coeruleus (LC), the brain's primary noradrenergic nucleus located in the pontine brainstem, has traditionally been associated with wakefulness. However, recent studies have revealed that the LC remains active during non-rapid eye movement sleep (NREMS), exhibiting fluctuations on infralow timescales. These dynamics correlate with a range of cortical, subcortical, and peripheral measures, and have been shown to gatekeep the NREM-to-rapid eye movement sleep (REMS) cycle, as well as generate distinct forms of arousal during NREMS. Despite this, the specific circuits underlying these functions remain largely unknown. Given that LC neurons differ in genetic origin, electrophysiological properties, and projection targets, we examined the activity of four major projection-defined LC populations during undisturbed sleep in freely sleeping mice. To selectively label these populations, we injected a retrograde Cre-expressing virus into the dorsal CA1 (dCA1), medial prefrontal cortex (mPFC), sensory thalamus, and basolateral amygdala (BLA), enabling GCaMP8s expression in the corresponding LC neurons. We then performed fiber photometry recordings across the 12-hour light phase, combined with polysomnography to monitor vigilance states. Although the targeted projection neurons were distributed along different dorsoventral locations within the LC, preliminary findings suggest a largely uniform activity during sleep across all four groups of neurons. Mean activity levels during wake, NREMS, and REM sleep were comparable, as was their participation in the various types of arousals during NREMS. Future experiments will explore how different waking experiences (such as auditory fear conditioning) may shape projection-specific LC activity during subsequent sleep.

**Disclosures:** G. Foustoukos: None. A. Luthi: None.

**Poster**

**PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

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**Topic:** G.07. Biological Rhythms and Sleep

**Support:** NIH Grant MH12814004  
NIH Grant AG08220201  
Wu Tsai Grant KCG-113

**Title:** Rem sleep readiness and duration are encoded during nrem by spinal-projecting sld neurons.

**Authors:** \*E. SEIGNEUR, L. DE LECEA;  
Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

**Abstract:** Rapid transitions between non-REM (NREM) and REM sleep are governed by a mutually inhibitory “flip-flop” switch between REM-on and REM-off neurons. While transitions are thought to be driven by accumulating REM sleep pressure, the neural mechanisms encoding this pressure remain poorly understood. Here, we identify a novel subpopulation of neurons in the sublaterodorsal (SLD) nucleus projecting to the cervical spinal cord (SLDsp) that signals REM sleep readiness in mice. Unlike typical REM-promoting neurons, SLDsp neurons are *inactive* during REM sleep (REM-off). Instead, their activity during NREM sleep robustly predicts both the likelihood of an upcoming NREM-to-REM transition and the duration of the subsequent REM bout. SLDsp activity also dynamically reflects REM sleep pressure, as increased pressure decreased the temporal dynamics and activity threshold preceding REM transitions. Optogenetic activation of SLDsp neurons during NREM significantly increased REM sleep, while chemogenetic inhibition suppressed REM transitions, even under heightened REM pressure. Furthermore, targeted ablation of SLDsp neurons disrupted REM sleep homeostasis, induced hyperarousal, hindered recovery after sleep deprivation, and impaired memory consolidation. Our findings reveal that SLDsp neurons function as a key signaling mechanism, indicating the brain’s readiness for REM sleep during NREM and encoding the upcoming REM bout’s duration. This demonstrates for the first time that REM duration is preemptively determined, and that aspects of REM sleep structure are directly embedded within NREM sleep. This novel mechanism provides a crucial link for how REM sleep pressure governs the NREM-to-REM switch.

**Disclosures:** E. Seigneur: None. L. de Lecea: None.

**Poster**

**PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.14/AA10

**Topic:** G.07. Biological Rhythms and Sleep

**Title:** Chemogenetic activation of Parafacial GABAergic neurons increases NREM sleep and affects cognitive behavioral profiles in mice

**Authors:** \*N. W. GRABAU<sup>1</sup>, E. ORTIZ-FEDER<sup>1</sup>, D. KROEGER<sup>2</sup>;

<sup>1</sup>Anatomy, Physiol. and Pharmacology, <sup>2</sup>Anatomy, Physiol. and Pharmacol., Auburn Univ., Auburn, AL

**Abstract:** While sleep is essential for optimal cognitive functioning, the underlying mechanisms remain unclear. The Parafacial Zone (PZ) was recently identified as a Non-Rapid Eye Movement (NREM) sleep promoting region. We hypothesized that manipulation of sleep via chemogenetic activation of sleep-active GABAergic neurons in the PZ will increase sleep and affect memory, anxiety and depression-like states in mice. We transfected GABAergic neurons in the PZ of VGAT-Cre mice with an adeno-associated virus (AAV) carrying the gene sequence for the excitatory chemogenetic receptor hM3Dq. We then administered Clozapine-N-Oxide (CNO; 0.1, 0.3, 0.9 and 2.7 mg/kg, i.p.) to activate hM3Dq expressing PZ neurons, and analyzed sleep/wake states via EEG/EMG recordings. To assess the effects of sleep on mouse behavior, we divided the mice into three groups; 'normal sleep', 'sleep deprived' and 'extra sleep' groups. Extra sleep was induced by activating the hM3Dq expressing PZ neurons. Mice of all groups then underwent behavioral tests; Novel Object Recognition Test (NORT) for object memory, Forced Swim Test (FST) for depression-like symptoms, and Open Field Test (OFT) and Elevated Plus Maze (EPM) for anxiety-like behaviors. Sleep was manipulated for 4 hours before behavioral tests. Our preliminary results show that during the first 4 hours after CNO administration, NREM sleep was significantly increased in a dose dependent manner while REM sleep and wake were decreased. Analysis of the behavioral tests suggests that an acute increase of sleep before the FST increased depression-like symptoms, as mice spend low *%time swimming* compared to mice in the 'sleep deprived' and 'normal sleep' groups. This indicates higher levels of depression-like states. In the OFT, 'sleep deprived' mice showed an increase in *%time in center zone*, *frequency of crossing center zone*, and *total distance traveled in the empty arena*. Sleep-deprived mice also behaved similarly in the EPM with increased *%time in open arm*, *frequency entering open arm*, and *distance traveled in open arm*. Together, OFT and EPM results suggest that acute sleep deprivation may improve anxiety-like behaviors. In the NORT, mice in the extra sleep group demonstrated an exploration index (EI) of 73, suggesting increased memory performance following extra sleep. In summary, our preliminary results suggest that chemogenetic activation of PZ GABAergic neurons significantly increases NREM sleep while suppressing REM sleep. Moreover, we observed that increased NREM sleep improves memory performance but may not improve anxiety or depression-like behaviors in mice. Instead, acute sleep deprivation may reduce anxiety and depressive states.

**Disclosures:** N.W. Grabau: None. E. Ortiz-Feder: None. D. Kroeger: None.

## **Poster**

### **PSTR232: Sleep-Arousal Transitions: Hypothalamic and Brainstem Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR232.15/AA11

**Topic:** G.07. Biological Rhythms and Sleep

**Support:** R01 NS119597-01A1

**Title:** Examining functional connectivity among sleep-wake nuclei in rodents

**Authors:** \*M. ARAI<sup>1</sup>, B. HARVEY<sup>2</sup>, C. ANACLET<sup>4</sup>, N. P. PEDERSEN<sup>3</sup>;

<sup>1</sup>Univ. of California Davis, Davis, CA; <sup>3</sup>Neurol., <sup>2</sup>Univ. of California, Davis, Davis, CA;

<sup>4</sup>Neurolog. Surgery, Univ. of California Davis Sch. of Med., Davis, CA

**Abstract:** Sleep-wake disturbances are a hallmark of various neurological and psychiatric disorders, such as Alzheimer's disease and epilepsy. Understanding the interactions between sleep-wake nuclei is essential for uncovering the network dynamics underlying global brain states and their disruption in these disorders. While the roles of individual nuclei have been well-characterized, a comprehensive view of their functional connectivity remains limited. In this study, we examined the dynamic interactions among anatomically targeted sleep-wake nuclei. To assess the complex interactions, we implanted 16 electrodes in mice using a custom 3D-printed headset and recorded unit activity and local field potentials. Coherence and imaginary coherence were analyzed using Brainstorm, an open-source platform for neurophysiological data analysis. Effective connectivity was evaluated using the phase slope index, a measure that infers directionality based on phase differences across frequencies. The preliminary results showed that multi-site sleep-wake nuclei recording is feasible and that non-instantaneous (imaginary) coherence differs from overall (magnitude squared) coherence, implicating potential far-field contamination of field-potential recordings. Therefore, we subsequently performed silicon probe recordings to analyze current source density and unit activity in sleep-wake nuclei, including the parafacial zone (PZ). Our group has previously demonstrated the critical role of PZ neurons in sleep induction and maintenance. Specifically, we have shown that GABAergic neurons in the PZ actively sustain cortical slow wave activity and slow-wave sleep (SWS). Consistent with these findings, our preliminary results in postnatal day 12 (P12) rats revealed a current source in the PZ associated with the peaks of delta waves (0.5-4 Hz) and slow oscillations (0.5-1 Hz), detected in both the PZ and frontal cortex. These results support the role of the PZ in regulating slow-wave activity and provide insight into its functional connectivity. The established connectivity analysis method may also serve as a valuable tool for future investigations of neural circuits underlying sleep-wake states in rodent models of sleep-related disorders.

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## **Poster**

**PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.01/AA12

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** AHA Postdoctoral Award 25POST1361712

**Title:** Androgen receptor-expressing neurons in ventromedial nucleus of hypothalamus regulate metabolic homeostasis

**Authors:** \*Y. DENG, C. WANG, Y. XU;  
Baylor Col. of Med., Houston, TX

**Abstract:** Androgen receptor (AR) signaling is involved in the regulation of glucose and metabolic homeostasis with a striking sexual dimorphism. In men, testosterone deficiency is closely associated with obesity and type II diabetes (T2D), and testosterone therapy in obese males with testosterone deficiency produces significant and stable weight loss. On the other hand, in women with polycystic ovary syndrome (PCOS), androgen excess and obesity are interconnected, with androgen excess contributing to weight gain and obesity exacerbating PCOS symptoms. However, the mechanism through which AR signaling differentially regulates metabolism in both sexes is not fully understood. In the current study, we re-analyzed a published single-cell RNA sequencing data set and found that AR-expressing neurons in the ventromedial nucleus of the hypothalamus (VMH) contained distinct neuron subpopulations between males and females. Thus, we hypothesize that AR-expressing neurons in the VMH regulate metabolic homeostasis in both sexes. Interestingly, long-term inhibition of AR-expressing VMH neurons in female mice led to a significant obese phenotype, including increased food intake and body weight, altered body composition, and impaired glucose homeostasis. In comparison, inhibition of VMH AR neurons in males produced moderate body weight and food intake increases without affecting glucose metabolism. In all, we concluded that normal VMH AR neuron activity is required to maintain metabolic and glucose homeostasis in both sexes. Future studies will focus on the metabolic role of AR signaling in VMH AR neurons and how it differs between males and females.

**Disclosures:** Y. Deng: None. C. Wang: None. Y. Xu: None.

## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.02/AA13

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** NRF-2021R1C1C2005067

**Title:** Alpha2-adrenergic receptors in hypothalamic dopaminergic neurons: Impact on food intake and energy expenditure

**Authors:** \*B. PARK<sup>1</sup>, H. YANG<sup>1</sup>, M. KIM<sup>1</sup>, J. KIM<sup>2</sup>;

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**Abstract:** The adrenergic system plays an active role in modulating synaptic transmission in hypothalamic neurocircuitry. While  $\alpha 2$ -adrenergic receptors are widely distributed in various organs and are involved in various physiological functions, their specific role in the regulation of energy metabolism in the brain remains incompletely understood. Herein, we investigated the functions of  $\alpha 2$ -adrenergic receptors in the hypothalamus on energy metabolism in mice. Our study confirmed the expression of  $\alpha 2$ -adrenergic receptors in hypothalamic dopaminergic neurons and assessed metabolic phenotypes, including food intake and energy expenditure, after treatment with guanabenz, an  $\alpha 2$ -adrenergic receptor agonist. Guanabenz treatment significantly increased food intake ( $0.25 \pm 0.03$  g vs.  $0.98 \pm 0.05$  g,  $p < 0.001$ ) and **body weight ( $-0.1 \pm 0.04$  g vs.  $0.33 \pm 0.03$  g,  $p < 0.001$ ) within 6 hours post-treatment. Furthermore, guanabenz markedly elevated energy expenditure parameters, including respiratory exchange ratio (RER,  $1.017 \pm 0.007$  vs.  $1.113 \pm 0.03$ ,  $p < 0.01$ ) and carbon dioxide production ( $(1.512 \pm 0.018$  ml/min vs.  $1.635 \pm 0.036$  ml/min,  $p < 0.05$ ), compared to vehicle-treated controls. Furthermore, using chemogenetic techniques, we demonstrated that the altered metabolic phenotypes induced by guanabenz treatment were effectively reversed by inhibiting the activity of dopaminergic neurons in the hypothalamic arcuate nucleus (ARC) using a chemogenetic technique. Our findings suggest functional connectivity between hypothalamic  $\alpha 2$ -adrenergic receptor signals and dopaminergic neurons in metabolic controls.**

**Disclosures:** B. Park: None. H. Yang: None. M. Kim: None. J. Kim: None.

## Poster

### PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.03/AA14

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** NIH Grant DK134609

**Title:** Dorsal hippocampal regulation of feeding structure

**Authors:** \*T. QI<sup>1</sup>, C. KRULL<sup>2</sup>, V. LEUNG<sup>4</sup>, D. YANG<sup>2</sup>, N. LAL<sup>2</sup>, J. MA<sup>6</sup>, S. WANG<sup>2</sup>, H. SHEN<sup>7</sup>, A. ZHANG<sup>8</sup>, B. ZHAO<sup>5</sup>, S. HEYDARI SERADJ<sup>6</sup>, A. KENNEDY<sup>5</sup>, L. YE<sup>3</sup>;  
<sup>1</sup>Scripps Res. Inst., La Jolla, CA; <sup>2</sup>Scripps Res. Inst., San Diego, CA; <sup>3</sup>Scripps Res. Inst., San Diego, CA; <sup>4</sup>The Scripps Res. Inst., San Diego, CA; <sup>5</sup>The Scripps Res. Inst., La Jolla, CA; ; <sup>6</sup>UCSD, San Diego, CA; ; <sup>7</sup>The scripps research Insitute, La Jolla, CA; <sup>8</sup>Scripps, San Diego, CA.

**Abstract:** Animals exert precise control over food intake, a process organized by distinct neural circuits that orchestrate the initiation, maintenance, and termination of feeding. While previous research has focused predominantly on the brainstem and limbic systems, growing evidence suggests that higher-order brain regions, such as the dorsal hippocampus (dHPC), also play a critical role in feeding regulation. Although lesions in the dHPC have been shown to disrupt food intake, the specific circuits and neural dynamics underlying this effect remain poorly understood.

To address this gap, we employed activity marker screening, in vivo calcium imaging, projection-specific optogenetic manipulation, and high-resolution behavioral phenotyping to identify a novel hippocampal node involved in regulating the microstructure of feeding behavior. Using a novel inverse activity marker developed in our lab, we identified the dorsal subiculum (dSub) as a key hippocampal region inversely correlated with food intake. The dSub projects robustly to several extrahippocampal targets, including the mammillary body (MB). Optogenetic manipulation of the dSub-MB projection revealed its causal role in modulating feeding bout duration by terminating ongoing feeding episodes, without altering total food consumption. Through in vivo calcium imaging and detailed behavioral analyses, we found that dSub-MB activity increases at the end of feeding bouts and exhibits transient peaks during mid-bout interruptions. Notably, optogenetic activation of this pathway converted brief interruptions into full terminations, effectively truncating the feeding bout. Together, these findings reveal a previously uncharacterized hippocampal-subcortical circuit that contributes to the top-down control of feeding. This work expands current models of ingestive behavior to include cognitive brain regions and provides a novel framework for understanding the interplay between hippocampal function and metabolic regulation.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.04/AA15

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** PSC-CUNY 52-268

**Title:** Conditioned Inhibition of Food Motivation in Obesity Prone and Resistant Rats

**Authors:** \*N. TU<sup>1</sup>, C. R. FERRARIO<sup>2</sup>, A. R. DELAMATER<sup>3</sup>;

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**Abstract:** Theories of Pavlovian conditioning have described phenomena where animals learn to respond to cues that signal reward, while also abstaining from responding when cues signal the absence of anticipated rewards (Pavlov, 1927; Tobler, 2003). In the latter case, these cues may become a conditioned inhibitor, suppressing conditioned responses to the appetitive stimulus. This pattern of behavior is thought to result from negative contingencies between the conditioned stimulus (CS) and unconditioned stimulus (US) (Rescorla, 1969). Derman & Ferrario (2018) found that selectively bred obesity-prone rats show a greater sensitivity to the motivational effects of food cues that trigger food craving. To gain further insight into the motivational



processes involved, we investigated whether obesity-prone rats might also be less sensitive to appetitive inhibitory cues. Experiment 1 aimed to establish a sign-goal tracking procedure for studying conditioned inhibition and its varying expression in behavior. Our procedure produced conditioned inhibition but revealed no differences between obesity-prone and -resistant animals. We replicated this pattern in Experiment 2 using a more robust explicitly unpaired procedure (EUP), again finding no differences between animals with differing obesity propensities.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.05/AA16

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** HKRGC- GRF 14112523  
HKRGC- GRF 14113522  
HMRF Grant 09203236  
CUHK 7104252

**Title:** A limbic circuitry contributing to fat appetite and craving behavior

**Authors:** \*X. LIU<sup>1</sup>, Y. ZHU<sup>1,2</sup>, X. ZHAO<sup>1</sup>, W. YUNG<sup>2</sup>, Y. KE<sup>1</sup>;

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**Abstract:** The regulation of feeding behavior relies on a complex neural network that integrates homeostatic needs with environmental and sensory cues. Among these, the hedonic drive for high-fat foods contributes substantially to overconsumption and obesity. While the neural circuits underlying general feeding behavior have been extensively studied, the mechanisms driving nutrient-specific appetites, such as fat craving, remain largely unknown. Here, we present evidence that the dorsal bed nucleus of the stria terminalis (dBNST), a key limbic structure, plays a central role in regulating fat-specific appetite. We found rats exhibited a robust preference for a high-fat diet (HFD) in both sated and hungry states, with high-fat consumption selectively enhancing neuronal activity in the dorsal bed nucleus of the stria terminalis (dBNST). Optogenetic stimulation of dBNST neurons in sated rats evoked rapid and selective fat-seeking behavior without significantly affecting intake of other nutrients. Conversely, chemogenetic inhibition of dBNST markedly reduced HFD overconsumption in rats subjected to an intermittent HFD paradigm. Furthermore, retrograde tracing from dBNST identified substantial input from both the posterior cortical amygdaloid nucleus (PCo) and the central amygdala (CeA). Finally, by combining in vitro patch-clamp recordings with optogenetics, we found that dopamine modulates this pathway, indicating a neuromodulatory mechanism that may underlie acquired fat craving. Together, our findings reveal a novel dBNST-centered circuit that

integrates olfactory and dopaminergic signals to drive fat-specific appetite, providing new insights into the neural basis of maladaptive eating behaviors.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.06/Web Only

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** NIH Grant R01 HL177081-01A1  
NIH Grant R01 HL136520-04

**Title:** Exploring sex-specific responses to sodium depletion on sodium appetite in mice

**Authors:** \*D. N. SILBERSTEIN, G. SOMMER, M. J. GLASS, T. A. MILNER;  
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**Abstract:** Excess sodium consumption can lead to hypertension by increasing fluid retention and blood volume, impairing blood pressure control. Significantly, there are important sex differences in sodium-sensitive hypertension (SSH). Population studies demonstrate that blood pressure in women is more salt-sensitive, especially beginning at the time of menopause. Sodium intake control is one strategy to limit SSH, but in practice limiting sodium consumption can be difficult to manage. Given this context, elucidating the mechanisms of sodium intake may be of value. A classical model to study the regulation of sodium intake in rodents involves inducing a state of sodium depletion by combining a low-salt diet with injection of the diuretic furosemide and presenting animals with an unpalatable sodium solution, which is termed “sodium appetite.” Additionally, repeated bouts of sodium appetite results in progressively increasing sodium intake, termed “sensitization,” a form behavioral plasticity. However, sex differences in sodium appetite and sensitization are not well understood. In the current study, we compared sodium appetite and sodium appetite sensitization using a two-bottle choice preference test between water and a sodium chloride solution (0.2 M) in adult male and female C57BL6/J mice, a common laboratory strain used in neurobiology research. We found a sex difference in sodium preference following sodium depletion. Although both male (n=16) and female (n=16) mice showed increased sodium chloride preferences following sodium depletion, females showed a greater preference compared to males, despite both sexes showing similar intake patterns under baseline conditions. In contrast, both male (n=6) and female (n=6) mice showed similar increases in sodium preferences with repeated bouts of sodium depletion in the sensitization model. These results indicate that sex is an important variable in sodium appetite in the mouse. Future studies will investigate the role of neural circuits and gonadal hormones in sodium preferences across the sexes.

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**Poster**

**PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.07/BB1

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** NIHMHD U54 MD007600  
GM103642  
HRD-736019  
OISE-1545803  
DBI-1337284  
IOS-2217657

**Title:** Neural Downregulation of Serotonergic Signaling During Aestivation in *Biomphalaria glabrata*

**Authors:** \*A. RIVAS JIMENEZ<sup>1</sup>, N. COLON SANTIAGO<sup>1</sup>, M. W. MILLER<sup>2</sup>;  
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**Abstract:** Aestivation is an ecological phenomenon in which snails and other animals enter a state of dormancy in response to drought. This behavior enables species like the freshwater pulmonate snail *Biomphalaria glabrata* to survive prolonged periods of environmental stress. Notably, *B. glabrata* serves as the intermediate host for *Schistosoma mansoni*, the trematode responsible for schistosomiasis, a disease affecting over 200 million people worldwide, particularly in rural areas of developing countries. Understanding how *B. glabrata* aestivates is of epidemiological interest, as this dormancy may facilitate long-term parasite survival and hinder disease containment efforts. While prior studies have focused on the metabolic consequences of aestivation, little is known about its effects on the central nervous system (CNS). In this study, we examined CNS adaptations in uninfected, aestivated *B. glabrata* using immunohistochemistry. Snails were maintained in a moist incubator ( $90 \pm 1\%$  humidity;  $23.5 \pm 1^\circ\text{C}$ ) for 30 days to induce aestivation. Whole-mount preparations were processed using standard protocols and labeled with antibodies against serotonin. Confocal microscopy revealed that all major serotonergic neuron clusters identified in active snails, including those in the cerebral, pedal, parietal, and visceral ganglia, were anatomically preserved during aestivation. However, serotonin-like immunoreactivity was markedly reduced across all ganglia, with diminished staining intensity and fewer detectable fibers. Given serotonin's key role in locomotion, arousal, reproduction, and sensory processing, these results suggest that downregulation of serotonergic signaling contributes to the CNS suppression and behavioral

inactivity observed during aestivation. Therefore, this work provides novel insight into neurochemical adaptations that may support survival in extreme environments.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.08/BB2

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:**               SECIHTI 1078765  
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**Title:** Impact of a high-fat diet on the motor behavior and its connection with the brain-derived neurotrophic factor and the huntingtin.

**Authors:** \*K. HERNANDEZ-BALDERAS<sup>1</sup>, V. M. RUIZ-RODRÍGUEZ<sup>4</sup>, C. GALINDO<sup>1</sup>, A. O. CUELLAR SANTOYO<sup>2</sup>, O. A. PATRÓN SOBERANO<sup>5</sup>, A. M. ESTRADA SANCHEZ<sup>3</sup>; <sup>2</sup>Biología Mol., <sup>3</sup>División de Biología Mol., <sup>1</sup>IPICYT, San Luis Potosí, Mexico; <sup>4</sup>Biología Mol., Inst. Potosino de Investigación Científica y Tecnológica, San Luis Potosí, Mexico; <sup>5</sup>Mol. Biol., Inst. Potosino de Investigación Científica y Tecnológica A.C., San Luis Potosí, Mexico

**Abstract:** High-fat diets, which are defined by a high proportion of calories coming from fats, have been linked to metabolic disorders and, more recently, to adverse changes in the brain. In animal models, evidence indicates that prolonged consumption of high-fat diets can lead to impaired synaptic plasticity, cognitive decline, and motor impairments. The latter may be linked to a decrease in brain-derived neurotrophic factor (BDNF) in the motor cortex, a brain structure that is essential for motor control. Given that huntingtin (HTT) is a crucial protein associated with BDNF transcription and its transport from the cortex to the striatum via the cortico-striatal pathway, the prolonged consumption of a high-fat diet may impact HTT. Thus, in this research work, we evaluated the impact of a high-fat diet (60% fat) on HTT content in the motor cortex and striatum, as well as the changes in motor behavior of C57BL/6 mice over an 8-week period. As it is well known that exercise increases BDNF expression levels in the cortex and striatum, we also evaluated the changes induced by the high-fat diet in animals that were allowed to swim for one hour five days a week, during the 8 weeks. Our results showed that mice that were fed with the high-fat diet had no changes in calorie intake or weight gain at 8 weeks of feeding. However, these mice exhibited a significant reduction in rearing behavior, suggesting that this behavior is particularly sensitive to dietary fat intake. In contrast, grooming behavior was increased in high-fat diet-fed mice compared to those that underwent exercise, indicating a potential anxiogenic or stereotypic effect induced by the diet. These behavioral changes support

the hypothesis that a high-fat diet induces alterations in brain areas that control motor activity, suggesting that key molecular pathways, including BDNF and HTT, may be affected.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.09/BB3

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** Research Incentive Funds (AMK)

**Title:** Community Brain Maps: Prototypes of a digital Brain Maps 4.0 with use cases for hypothalamic feeding control regions

**Authors:** \*I. ACEDO AGUILAR<sup>1,2</sup>, A. O. DELGADO<sup>2</sup>, S. E. HOLGUIN<sup>2</sup>, E. S. LANEAVE<sup>2</sup>, A. A. MARTINEZ<sup>2</sup>, J. A. SANDOVAL<sup>2</sup>, I. SALAZAR<sup>2</sup>, S. SILVA<sup>2</sup>, C. E. PORRAS<sup>2</sup>, S. I. SALAMAH<sup>2</sup>, A. M. KHAN<sup>1</sup>;

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**Abstract:** Now in its 4th edition, the *Brain Maps* open-access rat brain atlas by Dr. Larry Swanson (latest version, *Brain Maps 4.0* was published in 2018; *J Comp Neurol*), has long been an invaluable resource for the neuroscientific community. Digitization of this important resource to expand its capability as a community data portal has been reported as proofs-of-concept two decades ago, but has not been reported since that time. Here, we report the creation of a pair of prototype *Brain Maps* atlas environments that we provisionally call *Community Brain Maps*. These were created during the spring semester of 2025 in a software engineering practicum class for master-level students at The University of Texas at El Paso. Two teams were each tasked with developing a new digital version of *Brain Maps 4.0*. The teams developed a software application that transformed Swanson's original, high-resolution vector graphic rat brain atlas files into a digital interactive platform for brain structure navigation, region-specific neuroanatomical annotations, and literature exploration. Building upon the established atlas templates for the standardized representation of neuroanatomical data, the prototypes further enhance their utility by providing interactive navigation and a suite of integrated tools. The atlas can be viewed from 73 representative levels along its longitudinal axis where users can seamlessly toggle between viewing the color-coded regionalized template, gray and white matter delineations, the corresponding Nissl-stained section, and the overlaying stereotaxic and physical coordinate grids. The applications enable the selection of specific brain regions, the creation of user-specific notes, direct access to relevant scientific literature, Swanson's original footnotes, and a hierarchical view of the brain structure. Both versions display the .svg files of each one

atlas level and the regions inside each one, with a stereotaxic grid included to aid researchers performing intracranial operations. While replicating the functionality of a paper atlas, the software also enables novel search functions for existing scientific literature and the ability to save the results inside the atlas itself. These new versions of a Community Brain Maps will help democratize neuroanatomical research for this important animal model by making spatial datasets more widely available for scientific and educational use. We describe a workflow for its sustained growth and development through iterative buildouts each year in our annual course.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.10/BB4

**Topic:** G.08. Food and Water Intake and Energy Balance

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HHMI PERSIST Brain Mapping & Connectomics Lab  
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**Title:** A modern atlas in search of a boundary: Light Sheet Fluorescence Microscopy-based micro-to-mesoarchitectural mapping and density analysis of the rat hypothalamus

**Authors:** \***M. L. QUINTANA**<sup>1</sup>, J. ALVAREZ<sup>2,3</sup>, S. BALIVADA<sup>1</sup>, A. M. KHAN<sup>1</sup>;  
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**Abstract:** As Light Sheet Fluorescence Microscopy (LSFM) continues to expand the bounds of 3-D brain imaging, the development of an architecture-driven 3-D atlas is critical. Traditional atlases rely on thin-section Nissl staining, which is to date incompatible with 3-D staining protocols used in LSFM. Here, we identified NeuN as a viable Nissl proxy for cytoarchitectural delineation in whole brain tissue. Also, conventional 2-D atlases often overlook mesoarchitectural patterns due to limitations in section thickness, viewing angle, and plane constraint. Here, we address that limitation by analyzing 3-D optical sections at multiple thicknesses and presenting regional parcellation across all three standard planes of section. This multi-plane, multi-scale approach captures the volumetric continuity of cytoarchitecture and provides flexibility for stereotaxic applications critical to target complex regions like the hypothalamus. We present a NeuN-based, architecture-guided 3-D atlas of the rat hypothalamus

that leverages neuronal density patterns and mesoarchitectural continuity across multiple section thicknesses and planes to enable rigorous, LSM-compatible parcellation. Whole rat brains (n=3) were cleared and immunostained for NeuN using LifeCanvas Technologies' active staining protocols. Samples were then imaged with a SmartSPIM light sheet microscope, and the resulting volumes were rendered in 3-D using IMARIS. Cytoarchitectural features revealed by NeuN-positive cells guided the parcellation of hypothalamic subregions, which were contoured and volumetrically rendered. Optical sections were extracted in coronal, sagittal, and horizontal planes at varying thicknesses to facilitate multi-scale analysis. These optical sections enabled further evaluation of spatial distribution and neuronal density across hypothalamic subregions using nearest-neighbor interpolation. Incorporating sagittal and horizontal planes provided novel perspectives on several longitudinal structures, including the stria terminalis, periventricular zone, and medial forebrain bundle, which are often difficult to appreciate fully in conventional coronal atlases. Furthermore, subregions such as the anterior hypothalamic nucleus and ventral tegmental area exhibited prominent surface features in 3-D, allowing for more precise delineation of boundaries and a clearer understanding of how these regions abut adjacent structures. This work bridges the gap between classical histology and neuroanatomy, offering a new framework for micro-to-mesoarchitectural mapping of the brain while providing rich, spatially informative parcellation.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.11/BB5

**Topic:** G.08. Food and Water Intake and Energy Balance

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LSAMP PRELS Fellowship Program (LSA)  
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UTEP Research Incentive Fund (AMK)

**Title:** Functional mapping of lateral hypothalamic subregions during cue-potentiated feeding

**Authors:** \*V. I. NAVARRO<sup>1</sup>, L. MAYNEZ-ANCHONDO<sup>3</sup>, L. SIFUENTES<sup>1</sup>, L. SOTO ARZATE<sup>1</sup>, I. DELGADO<sup>1</sup>, I. A. MENDEZ<sup>2</sup>, A. M. KHAN<sup>1</sup>;

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**Abstract:** The lateral hypothalamic area (LHA) is a large, complex hypothalamic region with diverse functions along four major rostrocaudal divisions. Despite its size and heterogeneity,

disagreements over defining LHA subdivisions make characterizing its structure and function difficult. These subdivisions have distinct neuronal connectivity, suggesting they mediate different behaviors. Indeed, distinct LHA neuronal pathways are involved in rewarding responses, suggesting key roles in motivation, feeding, and cognition. Current anatomical classifications rely on chemoarchitecture or gene-directed manipulations but not on cytoarchitecture or connectivity data, which could provide a more functionally relevant, high-spatial-resolution map. Without precise distinctions, behavioral roles may be wrongly attributed to broad regions rather than specific populations. While the *Brain Maps 4.0* (BM4.0) atlas we use (Swanson, 2018; *J Comp Neurol*) offers a detailed cytoarchitectural map, the links between these divisions and distinct neurochemical, connectional, and behavioral features are still unclear. Cue-potentiated feeding (CPF), where food-predictive cues enhance feeding in the absence of hunger, offers a powerful behavioral model to study how LHA subdivisions integrate motivational and feeding signals. Within the LHA, GABAergic and MCH-immunoreactive neurons are of particular interest, as they are implicated in encoding reward cues and modulating cue-driven feeding via distinct pathways. In a pilot study with adult male rats, we validated our CPF paradigm, showing that the rats reliably distinguished between the CS+ and CS− cues. This was indicated by increased food approach behaviors and head entries during CS+ presentations, along with more food consumed compared to CS− trials. Ongoing analyses are examining how food cup-directed behavior varies across training sessions for each cue. We assess neuronal activation in LHA subdivisions through Fos immunoreactivity in response to food-paired cues. By mapping Fos expression onto cytoarchitectural boundaries in BM4.0, we aim to determine if specific LHA regions are selectively activated during the CPF paradigm. Future analyses will identify activated neuronal populations in the LHA and their neurochemical identities to better understand the circuits involved in CPF. By mapping functional activation to specific subregions, this work enhances our understanding of how hypothalamic circuits facilitate reward learning and motivated behavior.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.12/BB6

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** NIH Grant GM127251 to AMK  
HHMI PERSIST Brain Mapping & Connectomics Lab

**Title:** Neuroanatomical investigation of neuropeptidergic pathways in the rat brainstem encoding signals for pain and/or orosensory processing



**Authors:** \*J. PALACIOS, A. R. ARVIZU MORALES, G. P. TAPIA, S. BALIVADA, A. M. KHAN;  
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**Abstract:** Increased prescription of opioid medications has contributed to widespread misuse of drugs used for pain relief. Abuse of these drugs has the potential to disrupt food intake, reward processing and autonomic regulation. Non-opioid strategies for managing pain are actively being developed; however, our limited understanding of the spatial organization of neurochemical pathways underlying pain signaling is restricting our ability to identify novel therapeutic targets and how these might also intersect with feeding and autonomic control circuits. To address this issue, we surveyed the trigeminal nerve system, a key mediator of orofacial pain and orosensory processing, in a lower brainstem region crucial for autonomic functions. Using fixed and frozen 30-micron tissue sections from adult male Sprague-Dawley rats, we conducted a series of single- and double-label immunostaining experiments utilizing antibodies against the mu-opioid receptor (MOR), calcitonin gene-related peptide (CGRP), substance P (SP), and dopamine beta-hydroxylase (DBH). These key markers were selected to examine how pain- and/or feeding control-associated signaling mechanisms are architecturally arranged in the hindbrain and to better delineate potential points of convergence or crosstalk. Photomicrographs of the immunostained sections were aligned to those for an adjacent series of Nissl-stained tissue that served as cytoarchitectural reference for registration to a rat brain atlas (*Brain Maps 4.0*; Swanson, *J Comp Neurol*, 2018) (*BM4.0*). Using Adobe Illustrator, immunolabeled elements were manually traced at high resolution to generate detailed maps of the histology. Our immunohistochemical experiments, combined with spatial averaging algorithms, revealed a complex anatomical intersection between trigeminal nerve fibers and DBH+ cells, offering insights into the precise regions within the ventrolateral medulla where these fiber systems may be co-spatial or interacting with noradrenergic neurons, or located apart from them. Utilizing this atlas-based approach to further map the potential nodes of pain/feeding circuits, we can deepen our understanding of how nociception and orosensory signals might be processed in the brainstem, leading to more targeted approaches for pain modulation and feeding control.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.13/BB7

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** NIH Grant GM127251 to AMK  
HHMI PERSIST Brain Mapping & Connectomics Lab

**Title:** Chemoarchitectural analysis of the gut-brain peptide cholecystokinin in the hindbrain feeding network

**Authors:** \*D. RUBIO, A. MIN, G. P. TAPIA, S. BALIVADA, A. M. KHAN;  
Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

**Abstract:** Cholecystokinin (CCK) is a neuropeptide involved in regulating satiety and glucose homeostasis through its modulation of insulin secretion. The nucleus of the solitary tract (NTS) is a major sensory relay center in the brainstem that transmits a variety of visceral signals, with CCK serving as an important chemical messenger. Our mapping studies of the lower brainstem have reaffirmed how its organization is incredibly complex and contains many spatially overlapping chemical systems among its fiber inputs. To dissect the chemical architecture of key regions in the hindbrain, we used an antibody against CCK to label the dense cluster of CCK+ nerve terminals in the parabrachial nucleus (PB) along with CCK+ cell bodies in the nucleus of the solitary tract (NTS), utilizing multiple visualization methods to localize the immunoreactivity. Using Adobe Illustrator, the CCK+ nerve plexus and adjacent white matter were traced to accurately register the histological data to a digital rat brain atlas (*Brain Maps 4.0*; Swanson, *J Comp Neurol*, 2018) (*BM4.0*). Consensus maps were generated among a cohort of animals to precisely localize the CCK+ distribution within the external lateral layer of the PB, as well as to localize the various CCK+ densities in the caudal medulla. We mostly observed CCK+ cell bodies situated along the dorsal border of the NTS. The digitized maps we present lay crucial groundwork for future efforts to precisely targeting major CCK pathways traversing through the lower brainstem, which could reveal valuable insights regarding how this neuropeptide interacts with key brainstem cell populations to influence glucose homeostasis and mediate satiety signals.

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## **Poster**

**PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.14/BB8

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** NIH Grant GM127251 to AMK  
HHMI PERSIST Brain Mapping & Connectomics Lab  
UTEP Research Incentive Fund (AMK)  
UTEP College of Science (SB)  
Dodson Grant (GPT)

**Title:** Spatial mapping of oxytocin fiber density distributions in the lower brainstem of the adult male rat: Evidence for subregional delineation of the dorsal motor nucleus of the vagus nerve (DMX)

**Authors:** \*S. ZAMORA, L. LUCERO, G. P. TAPIA, S. BALIVADA, A. M. KHAN;  
Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

**Abstract:** The dorsal motor nucleus of the vagus nerve (DMX) mediates several autonomic functions including respiration, gastrointestinal activity, and energy homeostasis. Recent findings published in collaboration with our lab suggested that a cluster of cells in the lateral edge of the DMX may be more responsive to oxytocin (OT) signaling than other DMX neurons (Edwards et al., 2024; Front Drug Delivery). These findings, along with previous anatomical evidence, suggest that the DMX may contain functional subdivisions related to specific visceral targets. To further explore this possibility, we performed atlas-based neuroanatomical mapping of OT-containing nerve fibers across several coronal levels of the lower brainstem. Hindbrain tissue was processed using an antibody against OT-associated neurophysin (PS38) and visualized using 3,3' diaminobenzidine (DAB)-based immunoperoxidase labeling. Sections were photographed at ×20 magnification under brightfield and darkfield illumination. Using white matter tracts as anatomical landmarks, the images of immunostained sections were precisely aligned to digital atlas templates from a standardized framework (*Brain Maps 4.0*; Swanson, *J Comp Neurol*, 2018) (*BM4.0*) OT-labeled fibers were digitally traced using Adobe Illustrator, and spatial averaging was performed across tracings from a cohort of subjects to identify zones with heavy OT-fiber input. The consensus maps revealed an OT-dense region localized to the lateral edge of the DMX. A second hotspot was observed in an area of the VLM known to correspond with a population of A1 noradrenergic neurons, a known target of OT fibers from the paraventricular nucleus of the hypothalamus. These data suggest the presence of OT-sensitive subdivisions not currently recognized in cytoarchitecture-based maps; thus, the OT-dense region of the DMX is suggested as the preliminary boundary for a new DMXl (lateral part). Further research is needed to clarify if the regional delineation of the DMX into medial, middle, and lateral subdivisions may correspond to organ-specific effects linked with activation of distinct anatomical subregions.

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## **Poster**

**PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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UTEP SMART MIND Program – NIH Grant R25DA033613 (ARAM)  
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MERITUS Program - Campus Office for Undergraduate Research/Office  
of the Provost (ARAM)

**Title:** Neuroanatomical organization of the GLP-1 cell column and its spatial relationship with feeding-associated brainstem pathways

**Authors:** \*G. P. TAPIA, A. R. ARVIZU MORALES, M. L. QUINTANA, S. BALIVADA, A. M. KHAN;  
Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

**Abstract:** Pre-clinical models for studying the neural control of energy balance are critical tools for testing new blood sugar and weight management treatments. However, the lack of standardized atlas-based references that register key circuits within three-dimensional (3-D) space, impedes our ability to streamline analysis of how new Type 2 diabetes and obesity treatments affect these pathways. Building on our high-spatial resolution mapping of hindbrain hunger circuits, we utilized coronally sliced brainstem tissue and an antibody against glucagon-like peptide 1 (GLP-1) to systematically tabulate GLP-1<sup>+</sup> cells across the rostrocaudal extent of their spatial distribution. Repeating this process in n = 6 subjects allowed us to apply spatial-averaging algorithms to the recordings, generating consensus maps of the observed GLP-1 immunoreactivity. To evaluate the GLP-1<sup>+</sup> anatomy in a 3-D context, we performed whole-tissue immunolabeling and light sheet fluorescence microscopy on intact brainstem samples. Imaris software was used to navigate the volume renders of the 3-D samples, and optical sections were captured in multiple anatomical planes. Visualization in the horizontal plane revealed an extensive column of GLP-1<sup>+</sup> cells distributed through the dorsomedial medulla, displaying a cell density greater than what we previously understood. A cohort of brains were then horizontally sectioned using a microtome and immunostained for GLP-1, which supported our 3-D findings. Overall, our 2-D maps rigorously map the spatial distribution of the GLP-1 cell population, placing it in register with standardized anatomical delineations and a common stereotaxic coordinate framework. The complex spatial relationships between GLP-1 pathways and other chemical messengers that influence feeding can be contextualized when their distributions are overlaid together at this anatomical location in an atlas reference space. The experiments detailed here provide new insights as to how the GLP-1<sup>+</sup> hindbrain neurons are structurally organized, serving as a crucial step towards our completion of a more detailed, atlas-based record of this clinically relevant cell group, laying critical groundwork for pre-clinical testing of therapies targeting GLP-1 signaling.

**Disclosures:** G.P. Tapia: None. A.R. Arvizu Morales: None. M.L. Quintana: None. S. Balivada: None. A.M. Khan: None.

## **Poster**

**PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

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SMART MIND to ARAM (NIH Grant R25DA033613)  
UTEP Research Incentive Fund (AMK)

**Title:** Towards mapping the glucoregulatory network: Proposing standardized anatomical delineations for hindbrain catecholaminergic cell populations in the adult male rat

**Authors:** \*B. S. ARSLAN<sup>1</sup>, A. R. ARVIZU MORALES<sup>2</sup>, G. P. TAPIA<sup>1</sup>, S. BALIVADA<sup>1</sup>, A. M. KHAN<sup>1</sup>;

<sup>1</sup>Biol. Sci., Univ. of Texas at El Paso, El Paso, TX; <sup>2</sup>Biol. Sci., Univ. of Texas at El Paso, EL PASO, TX

**Abstract:** Catecholaminergic (CA) neurons are crucial to facilitate the counterregulatory response to hypoglycemia and may participate in feeding control. We showed that CA neurons in the medulla are involved in the rapid counterregulatory response (G P Tapia et al., 2023; *J Clin Med*). However, the full distribution of these neurons has not been registered in a standardized framework, leading to the underutilization of preclinical diabetes or obesity models due to a lack of mapped therapeutic targets. Towards establishing a map of such targets, here we report delineating hindbrain CA cell populations within a standardized rat brain atlas (L W Swanson, *Brain Maps 4.0, J Comp Neurol.*, 2018) (BM4.0). We performed single- and double-label immunofluorescence staining experiments with antibodies against dopamine beta hydroxylase (DBH) and phenylethanolamine *N*-methyltransferase (PNMT). These allowed us to identify noradrenergic and adrenergic neurons, respectively. We imported photomicrographs of our immunostained sections into Adobe Illustrator, where we carefully aligned them with digital BM4.0 atlas templates. The histochemical data from a cohort of male rats were manually annotated and registered to BM4.0 using a high-spatial resolution approach to preserve the intricate distribution patterns we observed. By utilizing this approach at common hindbrain atlas levels, we applied spatial averaging algorithms to a set of digitally overlaid maps showing CA cellular distribution. The resulting consensus maps revealed clusters of immunopositive cells provisionally assigned to A1, A2, A5, A6, and A7 cell groups. To further distinguish A1 (DBH<sup>+</sup>/PNMT<sup>-</sup>) from C1 (DBH<sup>+</sup>/PNMT<sup>+</sup>) neurons in the ventrolateral medulla (VLM) we examined the double-labeled material. Our results show that the DBH immunoreactivity displayed the greatest density in the VLM at atlas levels 49 and 70 and was continuous throughout most hindbrain levels. In contrast, PNMT-immunoreactive cells were concentrated in posterior hindbrain levels and were mapped alongside the DBH neurons to identify the A1/C1 transition zone for the first time. The standardized mapping of cell groups in this study is a critical first step towards developing a more comprehensive preclinical model of the hindbrain glucoregulatory network, providing insight into the organization of cell groups involved in feeding control or the response to hypoglycemia that could be targets for rational therapies

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**Poster**

**PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

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**Topic:** G.08. Food and Water Intake and Energy Balance

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Imaging Core of the IBN Core Facility  
UTEP Research Incentive Fund (AMK)

**Title:** Evaluation of neuronal nuclear antigen as a cytoarchitectural proxy for a Nissl stain in the rat brainstem: Towards a 3-d cellular-resolution atlas compatible with light sheet fluorescence microscopy

**Authors:** J. ALVAREZ<sup>1,2</sup>, M. L. QUINTANA<sup>3</sup>, \*S. BALIVADA<sup>3</sup>, M. J. KENNEY<sup>3</sup>, A. M. KHAN<sup>3</sup>;

<sup>1</sup>Biol. Sci., Univ. of El Paso Texas, El Paso, TX; <sup>2</sup>El Paso Community Col., El Paso, TX; <sup>3</sup>Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

**Abstract:** Nissl staining remains a cornerstone of brain region delineation due to its ability to reveal cytoarchitectural features foundational to traditional 2-D atlases, such as Swanson's *Brain Maps 4.0* (2018, *J Comp Neurol*). However, its incompatibility with staining protocols required for 3-D whole-brain imaging via light sheet fluorescence microscopy (LSFM) presents a major barrier to developing comprehensive, volumetric rat brain atlases. To address this, we investigated the viability of Neuronal Nuclei (NeuN) immunolabeling as a proxy for Nissl in defining boundaries within the rat brainstem, a highly complex and underrepresented region in current volumetric atlases. Our approach involved parcellating NeuN-stained 30 µm-thick sections and NeuN-stained optical sections from a cleared brainstem (n=3), then comparing these against adjacent Nissl-stained sections. Regional definitions from NeuN labeling showed strong alignment with those from Nissl, particularly in subregions with distinct cell density and organization, such as the nucleus of the solitary tract, dorsal medial nucleus of the vagus, and the gigantocellular reticular nucleus. Additionally, NeuN staining captured both high and low intensity zones, each contributing to boundary identification and cytoarchitectural pattern recognition. These findings demonstrate that NeuN can reliably replicate key region-defining features in both thin and optically thick tissue preparations. Importantly, we identified region-specific differences in neuronal morphology, including density and spatial distribution, which further validated NeuN's utility as a global, architecture-revealing stain. The ability to observe

these patterns consistently across different section thicknesses and planes suggests a strong potential for NeuN to serve as the foundational stain for a 3-D brainstem atlas compatible with LSFM. Moreover, our findings underscore the importance of incorporating multi-modal approaches in neuroanatomical research, highlighting the synergistic potential of combining chemoarchitectural techniques with advanced imaging methodologies for comprehensive brain mapping. Establishing a fiducial marker-defining global stain compatible with LSFM not only provides the foundation for a comprehensive 3-D brain atlas but also proposes a method for voxel-based coordinates for stereotaxic targets, expanding the volumetric visualization of brain regions. Our findings support ongoing efforts to develop a voxel-based coordinate system for the rat brainstem that enhances spatial resolution and stereotaxic precision in future neuroanatomical studies.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

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**Topic:** G.08. Food and Water Intake and Energy Balance

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HHMI PERSIST Brain Mapping & Connectomics Lab  
MERITUS Award to ARAM (Campus Office for Undergraduate Research/Office of Provost)  
UTEP College of Science (SB)  
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**Title:** Localization in 2-D and 3-D of the accessory nerve nuclei in relation to hindbrain regions implicated in feeding and autonomic control: evidence in support of their inclusion in standardized maps

**Authors:** \*C. A. SEGOVIANO<sup>1</sup>, A. R. ARVIZU MORALES<sup>2</sup>, G. P. TAPIA<sup>1</sup>, S. BALIVADA<sup>1</sup>, A. M. KHAN<sup>1</sup>;

<sup>1</sup>Biol. Sci., Univ. of Texas at El Paso, El Paso, TX; <sup>2</sup>Biol. Sci., Univ. of Texas at El Paso, EL PASO, TX

**Abstract:** The accessory nerve (XI) nuclei refer to aggregates of cells in the central nervous system from which the accessory nerve originates. The accessory nerve can be subdivided into two distinct components: the spinal accessory nerve (SNA) and the cranial accessory nerve (CNA). There is significant disagreement over its classification as a cranial nerve, along with the precise locations of its member nuclei in the medulla oblongata and spinal cord. Some rat brain atlases have excluded the cranial accessory nuclei in the medulla and there are inconsistencies

between rat brain atlases in the distribution of XI neurons. Exclusion of the XI in the medulla may be due to the consideration of CNA as a caudal portion of the vagus nerve. Previous research regarding the localization of the SNA in rats varies regarding its longitudinal extent and location in coronal sections, contributing to the variation. To begin mapping the putative XI motor neurons, we performed optimization experiments for antibodies against choline acetyltransferase (ChAT) and the neuronal nuclear protein (NeuN). Employing these immunohistochemical markers in a combination of 2-D and 3-D visualization methods allowed us to observe these cell groups from various planes and vantage points to examine the ChAT+ cell columns. By localizing white matter tracts of key hindbrain cranial nuclei (X and XII), we precisely aligned digital brain atlas templates with our histochemical data, allowing us to accurately register the location of ChAT+ nerve pathways to a standardized framework (L W Swanson, *Brain Maps 4.0, J Comp Neurol*, 2018) (*BM4.0*). The data recorded from a group of subjects were spatially averaged to generate consensus maps, which suggested the standardized delineations for the XI nuclei in the caudal brainstem and cervical spinal cord. Our empirical results support the inclusion of XI in rat brain atlas maps and help resolve the inconsistencies found across current brain and spinal cord atlases.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR233.19/BB13

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** WesternU 1395  
NIH-NCI CA207287

**Title:** The cannabinoid CB<sub>1</sub> receptor inverse agonist/antagonist activates adenylate cyclase/PKA signaling pathway among other well-recognized intracellular emetic signals to evoke vomiting in least shrews (*Cryptotis parva*)

**Authors:** \*N. A. DARMANI<sup>1</sup>, Y. SUN<sup>2</sup>, L. BELKACEMI<sup>3</sup>, W. ZHONG<sup>3</sup>, Z. DAILY<sup>4</sup>;  
<sup>1</sup>Coll Osteo. Med. Pacific, Western Univ. Hlth. Sci., Pomona, CA; <sup>2</sup>Biomed. Sci., Coll Osteo. Med. Pacific, Western Univ. Hlth. Sci., Eastvale, CA; <sup>3</sup>Biomed. Sci., Coll Osteo. Med. Pacific, Western Univ. Hlth. Sci., pomona, CA; <sup>4</sup>Biomed. Sci., Coll Osteo. Med. Pacific, Western Univ. Hlth. Sci., Claremont, CA

**Abstract:** Potential intracellular emetic signals involved in cannabinoid CB<sub>1</sub> receptor inverse agonist/antagonist, SR141716A, were investigated. SR141716A (20 mg/kg, i.p.)-induced vomiting occurred via both central and peripheral mechanisms as it was accompanied by robust emesis-associated increases in: i) c-fos- and phospho-glycogen synthase kinase-3 $\alpha$ / $\beta$  (p-GSK-



3 $\alpha$  $\beta$ )- expression in the shrew brainstem dorsal vagal complex (DVC), ii) phospho-extracellular signal-regulated kinase<sub>1/2</sub> (p-ERK<sub>1/2</sub>) expression in both the DVC and jejunal enteric nervous system (ENS), iii) time-dependent upregulation of cAMP levels and phosphorylation of several protein kinases [protein kinase A (PKA; Ser338), protein kinase B (Akt; Ser473), GSK-3 $\alpha$ / $\beta$  (Ser21/9), ERK<sub>1/2</sub> (Thr202/204), and protein kinase C  $\alpha$  $\beta$ II (PKC $\alpha$  $\beta$ II; Thr638/641)] in the brainstem emetic loci, and iv) SR141716A-evoked emetic parameters were attenuated by diverse inhibitors/antagonists of: PKA (H-89), ERK<sub>1/2</sub> (U0126 and PD98059), GSK-3 (AR-A014418 and SB216763), phosphatidylinositol 3-kinase (PI3K)-Akt pathway (LY294002), phospholipase C (PLC; U73122), PKC (GF109203X), Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII; KN62), L-type Ca<sup>2+</sup> channel (LTCC; nifedipine and amlodipine), store-operated Ca<sup>2+</sup> entry (SOCE; YM-58483 and MRS-1845), inositol trisphosphate receptor (IP<sub>3</sub>R; 2-APB), ryanodine receptor (RyRs; dantrolene), the serotonin 5-HT<sub>3</sub> (palonosetron)-, and dopamine D<sub>2/3</sub> (sulpiride)-receptor antagonists, as well as the transient receptor potential vanilloid 1 receptor (TRPV1R) agonist resiniferatoxin (RTX). Our findings suggest that SR141716A causes vomiting via inverse-agonist action which involves phosphorylation of emesis-associated kinases including cAMP/PKA, ERK<sub>1/2</sub>, PI3K/Akt/GSK-3, PLC/PKC $\alpha$  $\beta$ II, and CaMKII, which depend upon Ca<sup>2+</sup> mobilization involving extracellular Ca<sup>2+</sup> entry via plasma membrane Ca<sup>2+</sup> channels (such as LTCC, SOCE, TRPV1R) and intracellular Ca<sup>2+</sup> release via IP<sub>3</sub>Rs and RyRs. Serotonin 5-HT<sub>3</sub>-, substance P neurokinin NK<sub>1</sub>-, and dopamine D<sub>2/3</sub> -receptors also participate in SR141716A-mediated vomiting.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

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**Program #/Poster #:** PSTR233.20/BB14

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** Intramural Research Program of the National Institute on Drug Abuse

**Title:** Feeding and risk-seeking behaviors are promoted by an inhibitory pathway from the Substantia Nigra pars reticulata to the Dorsal Raphe

**Authors:** \*M. BARBANO, H.-L. WANG, U. MOHAMMAD, O. ESPINOZA, M. F. MORALES;

Natl. Inst. on Drug Abuse, Baltimore, MD

**Abstract:** The dorsal raphe nucleus (DR) is best known for containing serotonergic neurons; however, it also contains other neuronal subtypes, including glutamatergic neurons that express the vesicular glutamate transporter type 3 (VGluT3). Our previous research demonstrated that DR-VGluT3 neurons form excitatory monosynaptic connections with a subset of ventral

tegmental area (VTA) dopaminergic neurons projecting to the nucleus accumbens. Activation of this circuit mediates reinstatement of cocaine-seeking behavior. To identify upstream brain structures regulating DR-VGluT3 neurons, we used a retrograde tracing approach and discovered a major input from GABAergic neurons (expressing the vesicular GABA transporter, VGAT) in the Substantia Nigra pars reticulata (SNr). Using a combination of optogenetics and behavioral testing, we examined the functional role of SNr-VGAT inputs to the DR in modulating risk-seeking and feeding behaviors. We injected viral vectors encoding channelrhodopsin-2 (ChR2), halorhodopsin (Halo), or enhanced yellow fluorescent protein (eYFP) into the SNr of VGAT-Cre mice and implanted optical fibers targeting the DR. Optogenetic activation of the GABAergic SNr-DR pathway reduced anxiety-like behavior, an effect that was blocked by GABA receptor antagonists. Furthermore, stimulation of this pathway decreased depression-like behavior and increased risk-seeking behavior. In contrast, inhibition of the pathway produced the opposite effect: increased depression-like behavior and reduced risk-seeking behavior. In addition, activation of SNr-VGAT inputs to the DR induced voracious feeding behavior in ChR2 mice, that even overcame conditioned taste aversion. Although general food motivation was not enhanced by DR release of GABA from SNr-VGAT inputs, blocking DR release of GABA from SNr-VGAT inputs in Halo mice impaired motivation to obtain food rewards. Together, these findings highlight a critical role for SNr GABAergic inputs to the DR in regulating risk-seeking and feeding behavior.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

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**Title:** Direct interoceptive input to the insular cortex shapes learned feeding behavior

**Authors:** \*Z. ZHAO<sup>1</sup>, M. BOLTON<sup>1</sup>, S. BERTO<sup>2</sup>, S. A. STERN<sup>3</sup>;

<sup>1</sup>Max Planck Florida Inst. for Neurosci., Jupiter, FL; <sup>2</sup>Neurosci., MUSC, Charleston, SC; <sup>3</sup>Max Planck Florida Inst. for Neuroscience, Jupiter, FL

**Abstract:** The insular cortex (insula) is an interoceptive hub, which senses internal states such as hunger, thirst, pain, and emotions. Interoceptive information arrives at the insula indirectly, either through the vagus nerve's connections or through peripheral hormonal signals to the hypothalamus. Previous studies, however, suggest that the insula directly senses internal states, but the mechanisms remain elusive. We identified a novel population of glutamatergic leptin receptor-positive (LepR+) cells with a unique morphology in the insula (INS<sup>LepR</sup>). Based on leptin's known role in signaling adiposity levels, we hypothesized that INS<sup>LepR</sup> neurons detect internal states and thus regulate food intake and body weight. Accordingly, we found that leptin administration in the insula increases intrinsic excitability of INS<sup>LepR</sup> cells, suppresses feeding, and reduces body weight. Moreover, optogenetic stimulation of INS<sup>LepR</sup> cells suppresses learned operant feeding and leads to avoidance in a real time place preference context. We also found that INS<sup>LepR</sup> neurons encode operant feeding bouts, and their activity is modulated specifically by hunger, but not thirst, states. Single-nuclei sequencing and ribosome profiling revealed that INS<sup>LepR</sup> is expressed on both Layer 6 neurons and on vascular cells, suggesting that leptin can be delivered directly through receptor-mediated transport through the blood brain barrier into the insula. INS<sup>LepR</sup> neurons form mainly local connections within the insula and an external projection to the basolateral amygdala (BLA), and optogenetic stimulation of BLA terminals also regulated learned operant feeding. Moreover, we found that administration of leptin alters insula neural dynamics in response to feeding, but not drinking, behavior, and reshapes the transcriptome, suggesting that internal state information provided by leptin is used by the insula to coordinate feeding behavior. Taken together, our data supports a model for direct interoceptive input to the insula, in which INS<sup>LepR</sup> cells integrate adiposity level signals to regulate feeding and body weight in a learned manner.

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## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

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**Title:** Effect of Rgs7bp knockout on diet-driven intake patterns and weight gain in mice.

**Authors:** \*S. SINGH<sup>1</sup>, P. C. BENSING<sup>3</sup>, K. TRINH<sup>2</sup>, K. A. MARTEMYANOV<sup>5</sup>, E. P. ZORRILLA<sup>4</sup>;

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**Abstract:** Obesity is a chronic disease that affects 108 million American adults. Current treatment options, though effective, require ongoing use and have side effects warranting new biological targets. We previously identified altered nucleus accumbens expression of the rat gene *Rgs7bp*, which encodes the regulator of G protein signalling 7 binding protein. GWAS have linked human *RGS7BP* variants to body mass index, body weight, smoking, and sleep-wake patterns. To determine a causal role for *Rgs7bp* in feeding or weight gain, we tested the hypothesis that *Rgs7bp* gene knockout (KO) alters body weight, composition, or food intake using *Rgs7bp* KO mice (n=16) and wildtype controls (WT; n=15). At 8 weeks, mice were single-housed and provided ad libitum 5TUM (TestDiet; 3.30 kcal/g; 10.4% fat) for 2 weeks via FED3 devices, then randomly assigned to one of 3 diet conditions: 1) continuous 5TUM, 2) continuous sweet-fat diet (palatable, 35% fat, 31% sucrose [kcal]; 4.18 kcal/g; Bio-Serv), or 3) intermittent sweet-fat (24h, 3d/wk) with 5TUM on non-access days. Relevant to chronotype, in the first 15 days of the study, WT mice ate more 5TUM pellets than KO during the first hour of the dark cycle, significant on day 5 (KO: 19 +/- 2, WT= 27 +/- 2 pellets) and 15 (KO: 19 +/- 2 pellets | WT= 30 +/- 4 pellets, but did not eat a greater proportion of their daily intake overall in the dark cycle, no significant genotype/diet effect was observed (WT: 9.76 +/- 0.25 kcal | KO: 10.08 +/- 0.50 kcal). Mice with cyclical access to SF diet ate significantly more on access days (KO=23.60 +/- 2.20 kcal, WT= 20.7 +/- 2.30 kcal) than ad lib SF or 5-TUM mice (5TUM: 14.0kcal SF: 16.52kcal ), significantly undereating on non-access days (KO= 9.60 +/- 1.07 kcal, WT =9.80 +/- 2.10 kcal) vs. (5TUM: 14.15kcal SF:16.22kcal). Accounting for baseline, there is a significant effect of genotype on body weight and % body fat 3 weeks into diet cycles. KO gained more weight than WT (WT: 3.87 +/- 0.56 g | KO: 6.13 +/- 0.40 g; p < 0.001). There was also a significant effect of diet which is attributed to SF mice being different from both 5TUM (p < 0.01) and CYC (p < 0.01) (5TUM: 7.11 +/- 1.17 % | CYC: 6.17 +/- 1.25 % | SF: 12.86 +/- 2.37 %). Interpellet intervals and meal sizes will be presented to identify the microstructure by which cycled mice ate more on access days. Body composition, through Echo-MRI every 3 weeks of the experiment, will also be shown to interpret Genotype differences in weight gain. Deletion of *Rgs7bp* reduced ad lib food intake at the dark cycle onset, but increased weight gain across different feeding conditions. The results support that *Rgs7bp* causally influences feeding and weight gain and warrant further study of its relevance to chronotype and obesity.

**Disclosures:** S. Singh: None. P.C. Bensing: None. K. Trinh: None. K.A. Martemyanov: None. E.P. Zorrilla: None.

## **Poster**

### **PSTR233: Ingestive Behavior and Homeostasis: Mechanisms, Circuits, and Anatomy**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR233.23/CC2

**Topic:** G.08. Food and Water Intake and Energy Balance

**Support:** R01 AA028879  
P60 AA006420  
R21 AA029498  
R01 DK070118  
R01 DK076896  
F31 DA026708  
R21 MH124036

**Title:** Genetic sequence and knockout studies of a role for *Rgs7bp* in obesity and high-fat liquid diet intake in a binge-like access mouse model

**Authors:** \*P. C. BENSING<sup>1</sup>, A. HAWLEY<sup>3</sup>, M. BRAVO<sup>4</sup>, E. M. FEKETE<sup>4</sup>, A. SUNDARESAN<sup>3</sup>, P. NATARAJAN<sup>3</sup>, N. TOON<sup>3</sup>, T. LOW<sup>3</sup>, J. FRIHAUF<sup>3</sup>, K. A. MARTEMYANOV<sup>5</sup>, B. E. LEVIN<sup>6</sup>, E. P. ZORRILLA<sup>2</sup>;

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**Abstract:** Obesity affects ~108 million American adults. Current medications require ongoing use and elicit side effects. *RGS7BP*, the gene encoding regulator of G protein signaling 7 binding protein, associated with BMI, body weight (BW), smoking initiation, and chronotype in human GWAS. We sought to determine causal relevance of the ortholog *Rgs7bp* in rodent models. In a polygenic rat model of vulnerability to high-fat-diet-induced obesity (DIO, n=23), *Rgs7bp* was under-expressed in the nucleus accumbens (Log2FC = -0.843, -0.857;  $p < .001$ ) and highly mutated vs. diet-resistant (DR, n=35) rats. Relations of variant alleles to *Rgs7bp* expression will be presented. In weekly BW and percent body fat (%BF) measures from *Rgs7bp* knockout (KO) (male (M): n=19, female (F): n=14) and wildtype (WT) mice (M: n=17, F: n=15), KO weighed less at P49 (KO: 18.59 +/- 0.37 g; WT: 19.38 +/- 0.46 g;  $p < 0.05$ ) and P56 (KO: 19.53 +/- 0.40 g; WT: 20.34 +/- 0.48 g;  $p < 0.01$ ), but were fattier (%BF) at P28 (KO: 9.9 +/- 0.2 %; WT: 9.0 +/- 0.2 %;  $p < 0.01$ ), P35 (KO: 10.9 +/- 0.4 %; WT: 8.9 +/- 0.3 %;  $p < 0.001$ ), P42 (KO: 11.8 +/- 0.4 %; WT: 8.6 +/- 0.4 %;  $p < 0.001$ ), P49 (KO: 11.0 +/- 0.3 %; WT: 7.7 +/- 0.3 %;  $p < 0.001$ ), and P56 (KO: 11.1 +/- 0.3 %; WT: 8.1 +/- 0.4 %;  $p < 0.001$ ). At 8 weeks, a subset of mice (KO M: n=9; KO F: n=6; WT M: n=7; WT F: n=5) were single-housed and assigned to two groups. Controls received *ad lib* chow (Teklad 2018; 3.1 kcal/g; 18% kcal fat) and water; the experimental group also received 2-hr binge-like access (3 d/wk) to a high-fat “Cream-Oil-Sugar” (COS) liquid diet (5.99 kcal/g; 72% fat by kcal). Results so far (2 wks) show COS mice, as expected, had increased intake (kcal) vs. controls during the COS “access” period ( $p < 0.001$ ), reduced intake in the 24-hr post-COS period ( $p < 0.001$ ), and no differences in intake in the next (24-48 hr) non-access period. During Week 1, COS intake was increased in KO (4.17 +/- 0.26 kcal) vs. WT (3.15 +/- 0.37 kcal;  $p < 0.05$ ); in contrast, genotype intake effects were not concurrently seen in chow controls (KO: 1.39 +/- 0.10 kcal; WT: 1.34 +/- 0.13 kcal). In Week 2, no genotype difference in COS intake (KO: 4.74 +/- 0.31 kcal; WT: 4.37 +/- 0.37 kcal) was seen. Genotypes did not differ in chow intake in post-access (COS mice: KO: 7.60 +/- 0.62 kcal; WT: 7.98 +/- 0.18 kcal; Controls: KO: 9.78 +/- 0.46 kcal; WT: 9.44 +/- 0.51 kcal), or non-access (COS mice: KO: 9.26 +/- 0.39 kcal; WT: 9.83 +/- 0.17 kcal; Controls: KO: 9.50 +/- 0.46 kcal; WT: 9.17 +/- 0.50 kcal). Further weeks of intake, BW, and %BF will be compared across Genotypes and Diet conditions. While additional data will be necessary to support our

hypotheses, our early results suggest a role for *Rgs7bp* in fat accumulation during development and initial high-fat diet intake.

**Disclosures:** P.C. Bensing: None. A. Hawley: None. M. Bravo: None. E.M. Fekete: None. A. Sundaresan: None. P. Natarajan: None. N. Toon: None. T. Low: None. J. Frihauf: None. K.A. Martemyanov: None. B.E. Levin: None. E.P. Zorrilla: None.

## Poster

### PSTR234: Amygdala and Its Partners in Fear Processing

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.01/CC3

**Topic:** H.01. Fear and Aversive Learning and Memory

**Support:** ERC Grant, no. 885192, BrainRedesign

**Title:** Conditioned and innate fear responses are mediated by basolateral amygdala *Ndnf*-expressing neurons

**Authors:** \*Y. MASTRODICASA<sup>1</sup>, F. FERMANI<sup>1,2</sup>, M. FRUTOS MARQUEZ<sup>1</sup>, R. KLEIN<sup>1</sup>; <sup>1</sup>Max Planck Inst. for Biol. Intelligence, Munich, Germany; <sup>2</sup>Behavioral and Mol. Neurobio., Univ. of Regensburg, Regensburg, Germany

**Abstract:** The basolateral amygdala (BLA) is an integration center that regulates responses to both positive and negative behavioral stimuli. Although it is primarily composed of excitatory pyramidal neurons (PNs), the role of local inhibitory microcircuits in modulating BLA activity and mediating amygdala-related cognitive processes remains poorly understood. In this study we characterize neuron-derived neurotrophic factor (NDNF)-positive neurons in the BLA and their role during fear-related behaviors. Firstly, we employed high-resolution RNA fluorescence *in situ* hybridization (RNA-FISH) to reveal that BLA<sup>Ndnf</sup> neurons are predominantly GABAergic, with 93.5% co-expressing *Gad1*. These neurons also express canonical neurogliaform cell (NGFC) markers such as *Reln*, *Lamp5*, and *Npy*, while showing little overlap with major interneuron subtypes (*Sst* and *Pvalb*), confirming that BLA<sup>Ndnf</sup> neurons represent a distinct interneuron population in the BLA. To explore their role during fear processing, we examined *cFos* expression following a contextual fear conditioning (CFC) paradigm. BLA<sup>Ndnf</sup> neurons exhibited significantly elevated *cFos* levels during fear acquisition, but not during fear recall, indicating selective activation by acute aversive stimuli. By performing *in vivo* Ca<sup>2+</sup> imaging we identified two distinct neural ensembles of BLA<sup>Ndnf</sup> neurons that encode negative stimuli during contextual fear conditioning and odour-induced innate fear. One ensemble exhibited reduced activity during fear conditioning and trimethylthiazoline (TMT, fox odour) exposure, while the second ensemble displayed increased activity. In line with these activity patterns, optogenetic loss-of-function experiments indicated that the activity of BLA<sup>Ndnf</sup> neurons was necessary to promote freezing in response to aversive stimuli. Monosynaptic Rabies tracing revealed significant inputs from the cortical amygdala to BLA<sup>Ndnf</sup> neurons, consistent with these neurons

playing a role in the regulation of odour-induced fear responses. These findings suggest that two ensembles of BLA<sup>Ndnf</sup> neurons differentially regulate aversive stimuli, both conditioned and innate, thereby contributing to the modulation of BLA microcircuits and shaping the overall response to negative states, ultimately influencing animal behavior.

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## **Poster**

### **PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.02/CC4

**Topic:** H.01. Fear and Aversive Learning and Memory

**Support:** NIAAA Intramural Research Program

**Title:** Dynamic Regulation of Fear Memory Formation by Dorsomedial Intercalated Amygdala Neurons

**Authors:** \*O. BUKALO, O. CARPENTER, H. BHAGWAT, S. ZIMMERMAN, V. OFFENBERG, A. MENDEZ, A. HOLMES;  
Natl. Inst. of Health, Natl. Inst. on Alcohol Abuse and Alcoholism, Rockville, MD

**Abstract:** Survival relies on the brain's ability to associate environmental cues with potential threats—a process mediated by neural circuits specialized in fear learning. Within the amygdala, intercalated cell (ITC) clusters—distinct populations of GABAergic neurons encircling the basolateral amygdala (BLA)—have emerged as key regulators of both fear expression and extinction. In this study, we investigate the role of the dorsomedial ITC (dmITC) cluster in shaping fear memory acquisition. Using a transgenic mouse model expressing Cre recombinase under the control of the FoxP2 promoter, we selectively targeted dmITC neurons. Fiber photometry calcium imaging in awake mice revealed robust dmITC activation in response to aversive foot shocks. Functional manipulations further clarified the contribution of this population: optogenetic silencing of dmITC during shock impaired fear memory formation, whereas optogenetic excitation during conditioning only weakly substituted for the unconditioned stimulus. In contrast, chemogenetic inhibition of dmITC during training enhanced fear retrieval and disrupted cue discrimination, consistent with a gating role for these neurons. Additional imaging showed that chemogenetic dmITC inhibition elevated activity in the lateral amygdala (LA) and amplified fear expression, supporting the idea that dmITC neurons filter incoming sensory signals to prevent the consolidation of weak or ambiguous aversive events. We are currently examining the role of convergent sensory thalamic and cortical inputs to the dmITC in fear acquisition. Finally, projection-specific inhibition of dmITC terminals targeting either the BLA or the ventromedial ITC (vmITC) revealed pathway-specific effects on fear expression and

recall. Together, these findings establish the dmITC as a critical modulatory hub within the amygdala, orchestrating fear learning through input- and output-specific mechanisms.

**Disclosures:** O. Bukalo: None. O. Carpenter: None. H. Bhagwat: None. S. Zimmerman: None. V. Offenberger: None. A. Mendez: None. A. Holmes: None.

## **Poster**

### **PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.03/CC5

**Topic:** H.01. Fear and Aversive Learning and Memory

**Support:** NRF Grant RS-2018-NR028477  
NRF Grant RS-2023-00271562  
NRF Grant RS-2023-00265883  
NRF Grant RS-2018-NR030947  
MFDS Grant RS-2024-00332645

**Title:** Inhibitory Plasticity in Amygdala Engram Neurons Gates Fear Memory Precision via ICER-Dependent GABA<sub>A</sub>R Regulation

**Authors:** \*H. LEE, K. PARK, J.-H. KIM;  
POSTECH, Pohang-si, Korea, Republic of

**Abstract:** Precise discrimination between threatening and neutral stimuli is essential for adaptive behavior and survival, yet the inhibitory mechanisms ensuring this specificity remain poorly understood. Here, we identify parvalbumin (PV) interneuron-mediated feedforward inhibition (PV-FFI) as a key modulator of engram cell (EN) activity that enables fear discrimination. Auditory fear conditioning selectively potentiates PV-FFI onto ENs in the lateral amygdala through postsynaptic upregulation of  $\alpha 1$  subunit-containing GABA<sub>A</sub> receptors (Gabra1), preventing inappropriate EN activation by non-threatening cues without disrupting responses to conditioned stimuli. In contrast, mice exhibiting generalized fear lack this PV-FFI potentiation. Mechanistically, this deficit is linked to upregulation of inducible cAMP early repressor (ICER), which suppresses Gabra1 expression and impairs inhibitory synaptic plasticity. Bidirectional manipulation of ICER levels in ENs directly modulates fear specificity: ICER overexpression impairs discrimination, while ICER knockdown enhances it. These findings reveal inhibitory synaptic plasticity at EN synapses as a critical mechanism for fear discrimination and identify ICER as a potential therapeutic target for treating fear overgeneralization in disorders such as PTSD.

**Disclosures:** H. Lee: None. K. Park: None. J. Kim: None.

## **Poster**



## **PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.04/CC6

**Topic:** H.01. Fear and Aversive Learning and Memory

**Title:** Functional diversity and sensory integration in the lateral and basal amygdala nuclei during stimulus processing

**Authors:** \*D. MAGYAR<sup>1,2,3</sup>, N. HAJOS<sup>4,3,5</sup>;

<sup>1</sup>Indiana Univ., Bloomington, IN; <sup>2</sup>Semmelweis Univ., Budapest, Hungary; <sup>3</sup>HUN-REN Inst. of Exptl. Med., Budapest, Hungary; <sup>4</sup>Psychological and Brain Sci., Indiana Univ. Bloomington, Bloomington, IN; <sup>5</sup>Gill Inst. for Neurosci., Bloomington, IN

**Abstract:** The basolateral amygdala (BLA), a central hub in the limbic system, plays a crucial role in the acquisition and storage of fear memories. Located in the temporal lobe, it receives diverse inputs from both cortical and subcortical regions and integrates these signals via its extensive connections, particularly with the thalamus and prefrontal cortex. Disruption of BLA activity has been shown to impair fear learning, emphasizing its importance in adaptive responses to threat. Understanding how the BLA encodes aversive stimuli is key to uncovering the neural mechanisms underlying anxiety and post-traumatic stress disorders. In our study, we performed 64-channel silicon probe recordings in awake head-fixed mice to monitor single-neuron activity in distinct amygdalar nuclei during repeated presentations of an auditory tone and a mild tail-shock. Using spiking properties and waveform characteristics, we separated principal neurons and fast spiking interneurons. Based on the stimulus-evoked responses, neurons were categorized to different groups: some showed transient activation, others exhibited sustained responses, and a subset was inhibited. We also observed stimulus selectivity, with some neurons responding exclusively to one stimulus, and others responding to both tone and tail-shock. When the tone and tail-shock were presented simultaneously, we found no additive effect—the combined response did not exceed that of the most effective individual stimulus. This suggests that the BLA processes converging sensory inputs in a non-linear manner. Together, our findings highlight the heterogeneity and integrative properties of amygdalar circuits in encoding complex aversive experiences.

**Disclosures:** D. Magyar: None. N. Hajos: None.

### **Poster**

## **PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.05/CC7

**Topic:** H.01. Fear and Aversive Learning and Memory

**Support:** NIMH DP2 MH122399  
NIMH R01 MH120162  
NIMH R56MH132959  
Brain Research Foundation Award  
Klingenstein-Simons Fellowship  
NARSAD Young Investigator Award  
McKnight Memory and Cognitive Disorder Award

**Title:** An amygdala to anterior hypothalamic circuit gates negative valence and stress vulnerability

**Authors:** \*Z. T. PENNINGTON<sup>1</sup>, A. N. MAHMUD<sup>2</sup>, A. LABANCA<sup>1</sup>, S. ABDEL-RAHEIM<sup>2</sup>, M. BACON<sup>2</sup>, P. SOMPOLPONG<sup>3</sup>, A. BAGGETTA<sup>1</sup>, Y. ZAKI<sup>2</sup>, B. KO<sup>2</sup>, Y. FENG<sup>1</sup>, Z. DONG<sup>2</sup>, A. SMITH<sup>4</sup>, P. J. KENNY<sup>1</sup>, D. J. CAI<sup>2</sup>;

<sup>1</sup>Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; <sup>2</sup>Neurosci., <sup>3</sup>Icahn Sch. of Med. at Mount Sinai, New York, NY; <sup>4</sup>Med. Univ. of South Carolina, Charleston, SC

**Abstract:** Prior adversity increases sensitivity to subsequent stressful events, but the causal underlying changes in brain circuitry are poorly understood. Here we harnessed unbiased whole-brain activity mapping to identify circuits that are functionally remodeled by prior adversity to support inflated representations of negative valence and stress sensitivity. This revealed that the anterior hypothalamic nucleus (AHN) - a region that to date has received little attention - displays heightened stress reactivity in previously stressed mice. This was accompanied by increased functional connectivity between the AHN and a threat-related limbic network. Using *in vivo* Miniscope imaging, we found that neuronal activity in the AHN encodes negative valence. Moreover, prior stress amplifies the proportion of valence-encoding AHN neurons. Providing causal support for the AHN's role in negative valence, stimulating AHN neurons enhances, and inhibiting their activity mitigates, sensitivity to stressful events. Lastly, silencing amygdala inputs to the AHN abolishes the ability of prior adversity to increase stress sensitivity. These findings define a key role of the AHN in gating negative valence signals from the amygdala and highlight a novel region that could regulate vulnerability to stressful events.

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**Poster**

**PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

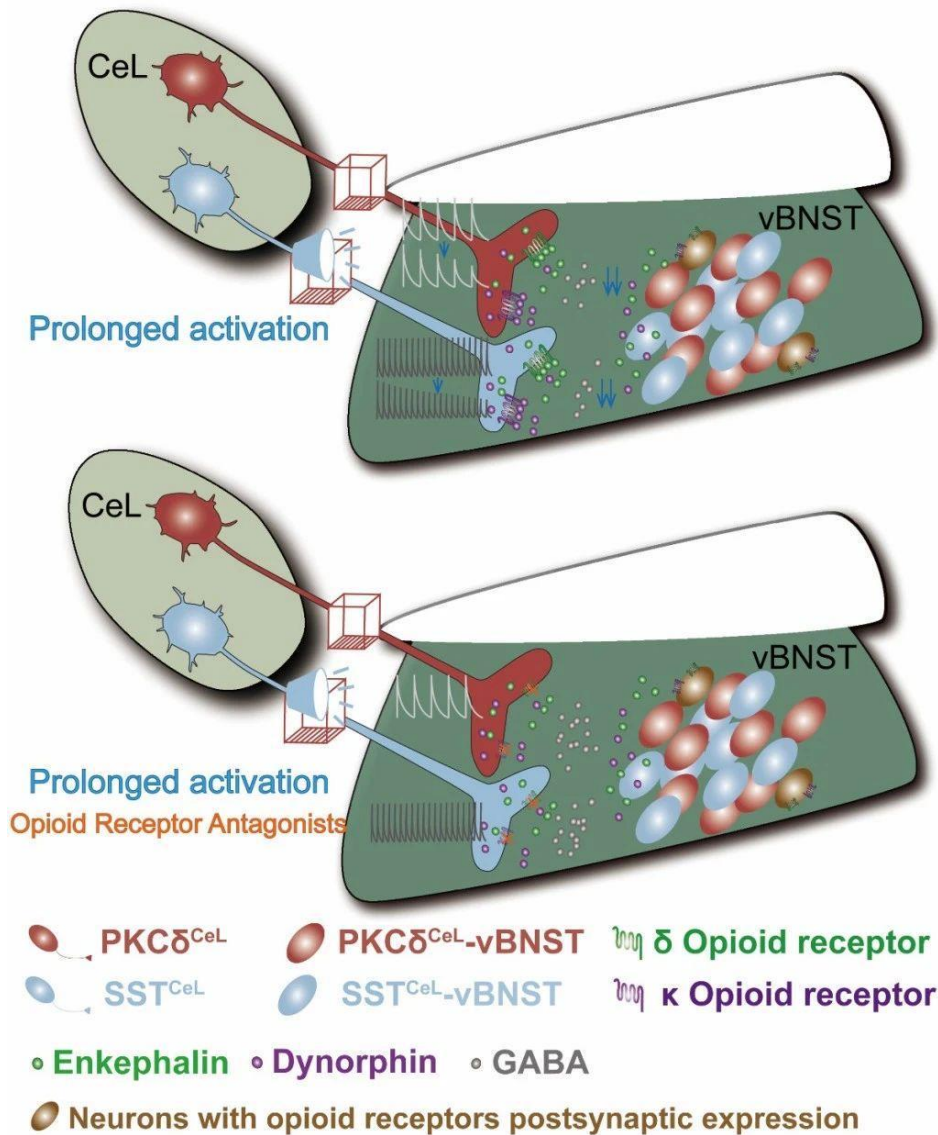
**Program #/Poster #:** PSTR234.06/CC8

**Topic:** H.01. Fear and Aversive Learning and Memory

**Title:** Distinct circuits from the central lateral amygdala to the ventral part of the bed nucleus of stria terminalis regulate different fear memory

**Authors:** \*A. PENG;  
Zhejiang Univ., Hangzhou, China

**Abstract:** We identified the projections from central lateral amygdala (CeL) protein kinase C  $\delta$  (PKC $\delta$ )-positive neurons and somatostatin (SST)-positive neurons to GABAergic (gamma-aminobutyric acidergic) and glutamatergic neurons in the ventral part of the bed nucleus of stria terminalis (vBNST). Prolonged optogenetic activation or inhibition of the PKC $\delta$ CeL-vBNST pathway specifically reduced context fear memory, whereas the SSTCeL-vBNST pathway mainly reduced tone fear memory. Intriguingly, optogenetic manipulation of vBNST neurons that received the projection from PKC $\delta$ CeL neurons exerted bidirectional regulation of context fear, whereas manipulation of vBNST neurons that received the projection from SSTCeL neurons could bidirectionally regulate both context and tone fear memory. We subsequently demonstrated the presence of  $\delta$  and  $\kappa$  opioid receptor protein expression within the CeL-vBNST circuits, potentially accounting for the discrepancy between prolonged activation of GABAergic circuits and inhibition of downstream vBNST neurons. Finally, administration of an opioid receptor antagonist cocktail on the PKC $\delta$ CeL-vBNST or SSTCeL-vBNST pathway successfully restored context or tone fear memory reduction induced by prolonged activation of the circuits.



**Disclosures:** A. Peng: None.

**Poster**

**PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.07/CC9

**Topic:** H.01. Fear and Aversive Learning and Memory

**Title:** A midbrain VIP-containing pathway controls potentiation of hippocampal inputs to the extended amygdala during contextual fear learning

**Authors:** \*M. KARLOCAI<sup>1</sup>, B. BARABAS<sup>2</sup>, K. MÜLLER<sup>3</sup>, J. M. VERES<sup>4</sup>, N. HAJOS<sup>5</sup>;  
<sup>1</sup>Gill Inst. for Neuroscience, Indiana Univ., BLOOMINGTON, IN; <sup>2</sup>Indiana Univ., Bloomington, IN; <sup>3</sup>Med. Univ. Innsbruck, Innsbruck, Austria; <sup>4</sup>HUN-REN Inst. of Exptl. Med., Budapest, Hungary; <sup>5</sup>Psychological and Brain Sci., Indiana Univ. Bloomington, Bloomington, IN

**Abstract:** Contextual fear learning is a mental process, during which an originally neutral context becomes associated with a threat. Previous data have shown that one of the main controlling units of the defensive system, the extended amygdala (EA) which includes the central amygdala (CeA) and bed nucleus of stria terminalis (BNST) is an active participant of contextual fear learning. Recently we discovered that vasoactive intestinal polypeptide (VIP)-expressing neurons in the ventral periaqueductal gray and dorsal raphe that innervate the EA play a role in contextual fear acquisition, but not in the recall and are activated upon salient stimuli. As the primary source of contextual information is the hippocampus, we aimed to uncover the synaptic mechanisms underlying midbrain VIP neuron-driven changes at ventral hippocampal (vHC) fibers in the EA. We hypothesized that VIP axon terminals from the midbrain would potentiate vHC inputs on EA neurons. In line with this prediction, we found that in 60% of in vitro recorded cells, synaptic potentiation was successfully induced by stimulating the vHC and midbrain VIP axons subsequently. Furthermore, we compared the AMPA/NMDA current ratio at vHC afferents in CeA and BNST neurons between fear conditioned and control animals and found a significant increase after fear learning. Moreover, reducing the activity of midbrain VIP neurons using chemogenetics prevented both the efficiency of contextual fear learning and the increase in the AMPA/NMDA ratio induced by fear learning. Potentiation of vHC-CeA synaptic transmission (measured as increased EPSC amplitude) could successfully be mimicked by bath applying 100 nM VIP and this effect was prevented by blocking type-2 VIP receptors. This indicates that plastic changes are probably induced by VIP released from midbrain axon terminals activating type 2 VIP receptors expressed in EA neurons. Our data thus show that the midbrain VIP inputs on EA neurons is necessary for contextual fear learning by potentiating the vHC synapses by increasing the AMPA/NMDA ratio via activating type 2 VIP receptors.

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**Poster**

**PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.08/CC10

**Topic:** H.01. Fear and Aversive Learning and Memory

**Title:** Effect of systemic oxytocin or selective activation of central amygdala OXTR-expressing neurons on cued fear expression in male and female rats

**Authors:** \*S. M. HO<sup>1</sup>, M. KANEKO<sup>1</sup>, K.-C. LEONG<sup>2</sup>;

<sup>2</sup>Dept. of Psychology, <sup>1</sup>Trinity Univ., San Antonio, TX

**Abstract:** Maladaptive fear can manifest into detrimental and debilitating effects, thus it is a concern that few pharmacological treatments exist for fear-related disorders. Previous studies in the literature and our published work show the neuropeptide oxytocin (OXT) has anxiolytic properties to combat stress, anxiety, and PTSD-like phenotype. The present study examines the effect of systemic OXT administration in attenuating cued fear expression in male and female rats and identifies the role of oxytocin receptors (OXTR) in the amygdala subnuclei, central amygdala and basolateral amygdala, in mediating this effect. Male and female Wistar rats ( $N = 53$ ) underwent a 2 day cued fear conditioning paradigm in which they received short, intermittent shocks (0.5 mA, duration of 1s) paired with a tone (20s, 80 dB) during the first day of the paradigm. On test day, freezing behavior was recorded as a measure of fear expression upon exposure to the fear-conditioned tone. In experiment 1, animals ( $n = 37$ ) received administration of either OXT (0.3 or 1 mg/kg, i.p.) or saline (i.p.) 45 minutes prior to testing. In experiment 2, OXTR-Cre<sup>+</sup> Wistar rats ( $n = 16$ ) received AAV-hSyn-DIO-hM3D(Gq)-mCherry infusion (0.5  $\mu$ L/side) into the central amygdala 21 days prior to fear conditioning. On test day, animals received administration of either CNO (3 mg/kg, i.p.) or saline (i.p.). To control for the potential effects of CNO alone, a separate group of naive animals with no viral infusion were tested with CNO (3 mg/kg; i.p.) alone. Overall, our results revealed that systemic administration of OXT has a limited effect on cued fear expression as analyzed using a one-way ANOVA. However, Cre-dependent DREADD-mediated selective activation of OXTR-expressing neurons in the CeA significantly attenuated cued fear expression in males and females. These findings highlight the importance of route of administration when investigating the therapeutic role of OXT on fear-related behaviors. Furthermore, these findings may also reveal a region-specific effect of OXT, via DREADD-mediated OXTR-expressing neuronal activation in the CeA, on fear expression. Further investigation should elucidate other regions that may be driving the limited effect of peripherally-administered OXT. Understanding this underlying mechanism behind OXT-mediated attenuation of fear expression can offer insight into route- and region-specific effects of its therapeutic role.

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**Poster**

**PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.09/CC11

**Topic:** H.01. Fear and Aversive Learning and Memory

**Support:** KAKENHI 22H04992

**Title:** Neural mechanism of retrospective fear induced by avoiding response to the optogenetic activation of collicular defense pathway

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**Abstract:** The James-Lange theory of emotion posits that emotions result from physiological reactions to external stimuli, suggesting that emotional experiences arise from retrospective interpretations of bodily states. However, the neural basis of this theory remains unclear. In our previous study, we showed that optogenetic activation of the descending pathway from the superior colliculus (SC) to the ipsilateral cuneiform nucleus (CnF) elicited various defensive behaviors in mice, suggesting a possible role for the SC-CnF pathway in emotional fear induction. Interestingly, SC-CnF neurons project collaterals to multiple brainstem nuclei connected to the amygdala. Based on this, we hypothesized that activation of the SC-CnF pathway may induce fear emotion coupled with defensive behaviors, which may support the James-Lange theory. To test this hypothesis, we performed a passive avoidance test in mice receiving optogenetic activation of the SC-CnF pathway. Stimulation in the dark chamber evoked defensive behaviors and increased latency to re-enter the dark chamber, suggesting fear memory formation. However, the behavioral response pattern did not correlate with memory strength, indicating that downstream motor circuits mediating defensive behaviors are distinct from those involved in emotional memory. Bilateral amygdala lesions abolished fear memory, confirming its critical role. To identify the pathway from SC to amygdala, we focused on the posterior thalamic triangular nucleus (PoT), known to relay aversive sensory signals to the amygdala. Anatomical tracing revealed robust bilateral input from SC-CnF neurons to the PoT, which projects to the amygdala. Using a double viral vector system to selectively block the PoT-to-amygdala pathway by express enhanced tetanus neurotoxin (eTeNT) resulting in a significant impairment of fear memory formation. This indicates that the SC-PoT-amygdala pathway is essential for emotional learning. Additionally, stimulation of the SC-CnF pathway also induced autonomic responses such as increased heart rate and pupil dilation. These responses were maintained despite amygdala lesions or PoT-amygdala pathway blockade, suggesting that autonomic responses are mediated by SC-CnF collaterals targeting other brainstem nuclei, rather than via the amygdala. Taken together, our findings demonstrate that fear emotion can be triggered by efference copies of motor commands through the collaterals of the SC-CnF neurons, supporting a revised interpretation of the James-Lange theory in which emotions arise centrally from efference copies of motor commands, independent of the long-loop feedback from bodily reactions.

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**Poster**

**PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.10/CC12

**Topic:** H.01. Fear and Aversive Learning and Memory

**Support:** NIMH-R01MH132018-01A1  
NSF-IOS 2137023

**Title:** The role of central amygdala-ventral tegmental area circuits in decision-making and ranked choice during learning.

**Authors:** \*R. FALLAHSABA<sup>1</sup>, O. M. OGUNDELE<sup>2</sup>;

<sup>1</sup>Comparative Biomed. Sci., <sup>2</sup>Louisiana State Univ., Baton Rouge, LA

**Abstract:** The central amygdala (CeA) and ventral tegmental area (VTA) form a critical circuit regulating reinforcement learning, decision-making, and approach-avoidance behaviors. While VTA and amygdala (CeA) are known to influence learning, the extent to which CeA-VTA pathways shape the balance between reward and aversion learning remains unclear. In this study, we investigated how the inhibition of CeA GABAergic projections in the VTA, as well as the VTA glutamate or dopamine-releasing terminals in the CeA, affects ranked choice decision-making in reinforcement paradigms. Neural projections were modulated using chemogenetic DREADDS, and its agonist Compound 21 (C21). In conditioned place preference and aversion tests, the target sides contained either 20% sucrose as the reward and a bitter-tasting mixture as an aversive stimulus. Double-floxed AAV5-DIO expressing hM4Di - an inhibitory GPCR - was injected into the CeA of VGAT-Cre mice while a cannula was positioned in the VTA. Similarly, in VGlut2<sup>Cre</sup> and TH<sup>Cre</sup> mice AAV5-DIO-hM4Di was injected into the VTA while a cannula was positioned in the CeA. For baseline preference (CPP) and aversion (CPA) tasks, animals were exposed to the reward and aversive stimulus without C21 modulation. After a wash period of 3 days, mice were tested in these tasks with chemogenetic modulation of CeA terminals in the VTA or VTA terminals in the CeA. Our results show that inhibiting CeA GABAergic terminals in the VTA enhanced reward learning but impaired aversion discrimination. Modulation of VTA terminals in the CeA had minimal impacts on reward or aversion learning. Notably selective modulation of VTA dopamine inputs caused modest changes in reward learning and mice maintained aversive responses. Furthermore, inhibiting VTA glutamate inputs to the CeA did not significantly change behavioral outcomes in both reward and aversion learning. Together, our results showed that CeA GABAergic modulation of the VTA plays a key role in balancing positive and negative valence in decision-making, shaping how organisms prioritize choices based on past reinforcement experiences.

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**Poster**

**PSTR234: Amygdala and Its Partners in Fear Processing**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR234.11/CC13



**Topic:** H.01. Fear and Aversive Learning and Memory

**Support:** SECIHTI CVU 1159410  
DGAPA IN227123

**Title:** Muscarinic antagonism after novel taste consumption causes conditioned taste avoidance related to diminished taste palatability and decreased posterior basolateral amygdala activation

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**Abstract:** Assigning valence to taste stimuli is essential for guiding ingestive decisions. The basolateral amygdala (BLA) contributes to emotional memory, yet the role of cholinergic neuromodulation in this process remains poorly understood. Here, we tested whether muscarinic signaling in the BLA affects the storage of the valence component of a taste. Male Wistar rats consumed 0.3% saccharin under a one-bottle attenuation of neophobia protocol. Immediately after the first exposure (S1), animals received either intra-BLA or systemic (i.p.) scopolamine. Ingestive behavior was recorded using a lickometer, analyzing volume, burst duration and interburst intervals (IBIs). Neuronal activation was assessed via cFos immunofluorescence with DAPI in anterior (BLAa) and posterior (BLAp). Scopolamine, both intra-BLA and i.p., blocked the normal increase in saccharin intake (attenuation of neophobia) and instead induced conditioned taste aversion, evidenced by reduced volume, shorter bursts, and increased IBIs at re-exposure. These effects were not observed with peripherally restricted N-butyl-scopolamine injections. At the neuronal level, scopolamine selectively reduced cFos expression in the BLAp, but not in the BLAa. In vehicle-treated rats, cFos levels in BLAa were unrelated to the amount of saccharin solution ingested by rats but did positively correlate with IBIs, suggesting a link between BLAa activity and taste palatability-related licking patterns. This result suggests that muscarinic receptors are needed for the assignment of positive valence to novel tastes. Disrupting this signaling not only prevents appetitive memory formation but actively shifts the affective value of the stimulus toward negative valence, resulting in a pharmacologically driven conditioned taste aversion. These findings highlight a critical role for cholinergic modulation in the BLA, particularly in the posterior subregion, in encoding the hedonic quality of gustatory experiences through both behavioral and neuronal mechanisms

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**Poster**

**PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.01/CC14

**Topic:** H.04. Emotion

**Support:** NIMH IRP

**Title:** Blindsight insight: Effect of unseen faces on macaque behavior and autonomic arousal

**Authors:** \***P. KUSMIEREK**<sup>1</sup>, C. J. BARTSCH<sup>3</sup>, E. A. MURRAY<sup>2</sup>;

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**Abstract:** Humans with damage to the primary visual cortex (V1) exhibit residual visual abilities, commonly known as “blindsight,” which challenge traditional models of visual processing (e.g., Weiskrantz et al, Brain 1974). In addition, affective stimuli (e.g., fearful or fear-conditioned faces) have been found to activate subcortical structures like the amygdala when presented in the blind portion of the visual field (scotoma), despite the fact that subjects deny conscious awareness of the images (Morris et al, Brain 2001). Similarly, when backward masking is applied to block awareness of briefly presented images in intact subjects, viewing of masked ‘unseen’ images of fearful faces or conditioned faces produces increased amygdala responses (Morris et al, Nature 1998, Whalen, J Neurosci 1998). These and related findings suggest that certain sensory cues may engage subcortical “defensive” circuits, bypassing cortical routes. Both human and nonhuman primate studies have implicated a colliculo-pulvino-amygdala route in threat detection (e.g., Bertini et al, Front Psychol 2018; Inagaki et al, Cereb Cortex 2022), but evidence from causal manipulations remains limited. Our study aims to identify specific anatomical substrates involved in threat-biased processing using a nonhuman primate model with V1 lesions. The behavioral paradigm was adapted from Bertini et al (2018). Rhesus monkeys were trained to perform a visual discrimination task: they used a joystick to differentiate between horizontal and vertical Gabor patches presented 10° from central fixation. Next, they underwent unilateral V1 aspiration lesions to produce a scotoma in the contralateral visual field. After mapping of the visual field defect, we presented images of fearful, neutral, and threatening monkey faces (or no stimulus) within the scotoma while monkeys performed the visual discrimination task with Gabor patches presented in the intact visual field. We assessed discrimination performance and whether the unseen face images influenced reaction time (RT) or autonomic responses (heart rate and pupil diameter). Preliminary results (N=2) show that after the V1 lesion discrimination accuracy remained high (typically >90%) across all conditions. RT averaged ~400-450 ms before and after surgery and gradually decreased to ~350-380 ms in postoperative testing. There was no significant effect of the affective face images on either RT or autonomic measures. Thus, under the current task conditions, affective faces presented in the scotoma do not modulate behavioral or physiological responses. Further work is needed to assess task sensitivity and explore other stimulus designs.

**Disclosures:** P. Kusmierek: None. C.J. Bartsch: None. E.A. Murray: None.

**Poster**

**PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.02/CC15

**Topic:** H.04. Emotion

**Support:** JSPS Grant-in-Aid for Research Activity Start-up, 24K23229  
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JSPS Grant-in-Aid for Scientific Research (A), 20H00104

**Title:** Anterior cingulate projections to basal amygdala subnuclei in primates: topographic and laminar architecture underlying emotion and mood regulation

**Authors:** \***K. KIMURA**<sup>1</sup>, **R. YOSHINO**<sup>1</sup>, **A. ZHENG**<sup>2</sup>, **S. NAKAMURA**<sup>1</sup>, **S. OHARA**<sup>1</sup>, **K.-I. INOUE**<sup>2</sup>, **M. TAKADA**<sup>3</sup>, **K.-I. TSUTSUI**<sup>1</sup>;

<sup>1</sup>Tohoku Univ. Grad. Sch. of Life Sci., Aoba-ku, Sendai City, Miyagi PREF, Japan; <sup>2</sup>Ctr. for the Evolutionary Origins of Human Behavior, Kyoto Univ., Inuyama, Japan; <sup>3</sup>Neurol., OSAKA UNIVERSITY, Suita, Osaka, Japan

**Abstract:** The medial frontal cortex (MFC) is interconnected with various brain regions involved in emotion. To elucidate the function of neural circuits related to emotion, it is essential to investigate the anatomical connectivity between them. The projections from the anterior cingulate cortex (ACC), a part of the MFC, to the amygdala are known to primarily target the basal nucleus, with no projections to the lateral or central nuclei of amygdala; however, certain details of these connectivity remain unclear. Here, we injected the retrograde viral vectors (AAV2retro) into different subnuclei of the amygdala and examined the distribution of labeled neurons within distinct ACC subregions. Retrograde tracing revealed that the basolateral amygdala receives robust projections mainly from the pregenual ACC (pgACC; area 24b and 32) and subgenual ACC (sgACC; area 25). The accessory basal amygdala was found to receive projections from the sgACC and the posterior part of the dorsal ACC (dACC; area 24a, b, c). Interestingly, while sgACC and dACC projected to the amygdalar subnuclei from layers V/VI, pgACC projected to the basolateral amygdala primarily from layers II/III. Additionally, we performed simultaneous injections of anterograde AAV vectors encoding multicolor fluorescent proteins into three distinct ACC subregions to confirm the results of the retrograde tracing. The anterograde tracing results also supported the findings from the retrograde tracing. These findings suggest that ACC subregions exhibit distinct projection patterns and laminar distributions to amygdala subnuclei, potentially playing the different roles in emotional system.

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**Poster**

**PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.03/DD1

**Topic:** H.04. Emotion

**Support:** NIMH Intramural Research Program

**Title:** Amygdala lesions fail to disrupt pupil-based arousal responses to threatening visual stimuli in macaque monkeys

**Authors:** \*J. HWANG, P. L. NOBLE, D. A. LUNDGREN, J. D. FLORES, E. A. MURRAY;  
Section on Neurobio. of Learning and Memory, Lab. of Neuropsychology, NIMH/NIH,  
Bethesda, MD

**Abstract:** The amygdala comprises a group of telencephalic nuclei thought to bias behavioral outputs to explore or exploit resources, avoid predators, produce progeny, and learn about sensory cues that signal resources, threats or safety. In macaques, one of the most robust and reliable effects of amygdala lesions is the reduction of defensive behaviors expressed in response to real or fake snakes. Macaques appear to recapitulate the physiological responses of humans to snakes and/or spiders, and research on its neural underpinnings may inform not only the neural bases of small animal phobias, but also the broader question of the neural circuits underlying implicit affective responses. In a previous study, we found that monkeys made faster responses to snake images when those images were the targets in an odd-one-out task (Hwang et al. SfN abstract, 2024). Relative to controls ( $N=4$ ), monkeys with amygdala lesions ( $N=3$ ) produced overall slower reaction times (RTs). Interestingly, the more snakes presented on the screen, the faster the RTs became. We hypothesized that this effect was due to increased arousal engendered by the array of snake images. To investigate further whether arousal was indeed modulated by the presence of snake images, we trained the same subjects with a fixation task that allowed us to monitor pupil diameter. During the task, four mask stimuli were presented—one on each quadrant of the screen around the center—and stayed on for the whole test session. When the monkeys gazed at the central fixation point for 400-600 ms, the masks changed to flower images. If the monkeys successfully maintained fixation for an additional 2 s, the images reverted to masks and a fluid reward was delivered. In some trials, snake images appeared instead of flower images. There were three experimental conditions: four flower images; one snake image/three flower images; and four snake images. The locations of the snake images were balanced within sessions. The size of the pupil was recorded with an eye tracker as a measure of autonomic arousal. To minimize effects of brightness on the pupil, masks and images were luminance matched. A mixed-model ANOVA revealed a significant main effect of the number of snakes ( $p<0.001$ ) but no interaction with the lesion group ( $p=0.35$ ). The pupil size decreased as the number of snakes increased from zero to one and four, and the monkeys with amygdala lesions did not differ from controls in their pattern of pupil size changes. Our results indicate that although predator images modulate arousal, the amygdala is not essential for this aspect of the affective response.

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## Poster

### PSTR235: Non-Human Primate Neural and Behavioral Processes

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.04/DD2

**Topic:** I.03. Decision Making

**Support:** HHMI  
Grossman Center for the Statistics of the Mind  
Air Force Office for Scientific Research (21RT0878)  
R01NS113113  
R01MH122513  
Kavli Center, Columbia University

**Title:** Single-trial dynamics of decision-related activity in the frontal eye field revealed by neuropixels recordings

**Authors:** \*N. SO<sup>1</sup>, A. ZYLBERBERG<sup>2</sup>, B. MADEIRA<sup>1</sup>, A. GHAZIZADEH<sup>1</sup>, M. N. SHADLEN<sup>3</sup>;

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**Abstract:** The neurobiology of perceptual decision-making has deepened our understanding of how the brain transforms sensory information into action. Prior studies in nonhuman primates have shown that single neurons in the oculomotor circuit, including the lateral intraparietal area (LIP), frontal eye field (FEF), and superior colliculus (SC), represent the accumulation of noisy evidence bearing on the saccadic choices (i.e., drift-diffusion). However, evidence for this assertion was adduced from trial-averaged responses, leaving open the possibility that the dynamics of single decisions are explained by another stochastic process that does not involve evidence accumulation. Using Neuropixels probes, we demonstrated that the response averages in LIP comprise drift-diffusion traces that mediate choice and reaction time (RT) on single decisions. The main projections of LIP are to FEF and SC. Stine et al. showed that the single-trial dynamics in SC are dominated by transient bursting events, which appear to play a role in terminating the decision. Until now, single-trial dynamics in FEF have not been characterized. Here we report preliminary findings from one monkey. We used high-density Neuropixels probes to record simultaneously from large populations of FEF neurons while the monkey performed a reaction-time version of the random dot motion discrimination task. We found that FEF populations encode decision variables with single-trial dynamics consistent with the accumulation of noisy samples. These dynamics closely resemble those observed in LIP using similar methods.

We also observed rich functional heterogeneity of decision-related neurons within the FEF. While some neurons exhibited stochastic dynamics consistent with evidence accumulation, others exhibited mainly motor-related activity. These subpopulations were identified by training population decoders, to (1) predict the monkey's choice or (2) the time of the saccade —What and When decoders, respectively. The vectors of weights define coding directions (CDs) in the

state space, which are orthogonal. Population activity projected onto the What CD, but not the When CD, yields the drift-diffusion decision variable. This is in stark contrast to LIP, where What and When coding directions are highly similar (Steinemann, Stine et al. 2023). Our ongoing effort is to characterize the functional and temporal relationships between signals in FEF, LIP, and other nodes of the macrocircuit.

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## **Poster**

### **PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.05/DD3

**Topic:** H.04. Emotion

**Support:** NIH IRP

**Title:** Anatomical Evidence for the Basolateral Amygdala (BLA) as a Hub for Distributing a Value Normalization Signal

**Authors:** \*W. LERCHNER<sup>1</sup>, C. CHANG<sup>2</sup>, B. LI<sup>3</sup>, B. J. RICHMOND<sup>4</sup>;  
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**Abstract:** Neural signals encoding reward value play a central role in assigning context-dependent salience to sensory stimuli during decision-making. It is widely assumed that this process relies on a distributed value normalization signal that coordinates priorities across sensory and reward-processing pathways. To identify neural populations that may distribute such a signal, we used retrogradely transported lentiviruses encoding fluorescent or epitope-tagged reporters to label projection neurons across multiple pathways involved in value and sensory processing. Three macaques received intra-hemispheric injections of FuGE-Lenti-hSyn::GFP and FuGE-Lenti-hSyn::mCherry into the orbital frontal cortex (OFC) and rostromedial caudate (rmCD), two areas implicated in reward-value processing. In a fourth monkey, these viruses were injected into anterior and posterior inferotemporal cortex (TE and TEO), while a third virus, FuGE-Lenti-hSyn::HA\_hM4Di, was injected into the posterior putamen/tail of the caudate (pPU/tCD), regions associated with sensory and visuomotor functions. Across all four animals, we observed clusters of co-projecting neurons in several regions potentially involved in value normalization, including the prefrontal cortex, temporal lobe, insular cortex, dorsomedial thalamus, and claustrum. However, the intermediate division of the basolateral amygdala (BLA) consistently contained the highest density of co-projecting neurons across all injection sites. For example, over 60% of BLA neurons projecting to the posterior putamen also projected to inferotemporal cortex, and up to 45% of those projecting to the OFC also sent axons to the ventromedial caudate. Further, the magnocellular BLA showed high co-projection to pPU/tCD

and IT cortex, while the parvocellular BLA showed co-projection to OFC and rmCD. These results suggest that the BLA, particularly its intermediate division, is anatomically positioned to broadcast a common signal via bifurcating axons to both reward and sensory pathways. This signal may serve as a candidate for normalizing value across context-dependent decision-making circuits.

**Disclosures:** W. Lerchner: None. C. Chang: None. B. Li: None. B.J. Richmond: None.

## **Poster**

### **PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.06/DD4

**Topic:** H.04. Emotion

**Title:** Reversible inactivation of the rostral periaqueductal gray impairs production of aggressive but not appeasing facial expressions

**Authors:** \*J. DILL<sup>1</sup>, D. CELDRAN-BONAFONTE<sup>2</sup>, K. M. GOTHARD<sup>4</sup>, A. J. FUGLEVAND<sup>3</sup>;

<sup>1</sup>Physiol., <sup>2</sup>Univ. Animal Care, <sup>3</sup>Dept. of Physiol., Univ. of Arizona, Tucson, AZ; <sup>4</sup>Physiol., Univ. Arizona, Col. Med., Tucson, AZ

**Abstract:** Humans and non-human primates use stereotyped facial expressions for socio-emotional communication. The motor pathways involved in the production of facial expressions are poorly understood. The prevailing view is that the genesis of emotional facial expressions depends on projections from various cortical areas to the facial motor nuclei in the pons, where the motor neurons reside. In contrast, the periaqueductal gray (PAG) has been identified as a crucial downstream node from the amygdala for producing similar stereotyped, innate behaviors - such as social vocalizations, defensive responses, freezing, escape, courtship, and maternal behaviors. We hypothesized, therefore, that an emotional state instantiated in the amygdala and warranting an expression engages the PAG. The PAG, in turn, activates pattern generating circuits in the brainstem to produce the most context-appropriate facial expressions. To test this hypothesis, we first recorded neural activity in the dorsolateral rostral PAG with a 32-channel microelectrode array while an adult female macaque made aggressive (threats) and appeasing (lip-smack) facial expressions to human experimenters. The monkey had also been trained to make voluntary facial actions (pursing of lips, opening mouth) that were not triggered by social-emotional stimuli. A subset of neurons in the PAG responded immediately prior to the production of threats but not during other types of facial movements. Moreover, following a microinjection of muscimol through a pore centered in the electrode array that silenced spiking activity of neurons in a 2.2 mm-diameter volume, the monkey could not be induced to make threats. The production of lip-smacks and voluntary facial actions, however, were unimpaired. The deficit of threat production persisted for at least 3 hours after the unilateral PAG injection

but returned to normal 24 hours later. These results indicate that rostral PAG in macaques actuates threatening facial expressions used during aggressive interactions.

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## **Poster**

### **PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.07/DD5

**Topic:** I.03. Decision Making

**Support:** R01MH132064

**Title:** Decoding choice dynamics from frontal cortex, striatum, and amygdala during probabilistic reasoning

**Authors:** \*N. VALLURU<sup>1</sup>, F. M. STOLL<sup>2</sup>, P. H. RUDEBECK<sup>3</sup>;

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**Abstract:** Dynamically navigating environments requires us to know the probabilities of certain reward outcomes given a particular choice. In probabilistic decision contexts, success hinges on accurately estimating the likelihood that an option will yield a favorable result. Single neurons in the prefrontal cortex (PFC) and amygdala have both been implicated in encoding reward probability, but it remains unclear how populations of neurons in these regions dynamically represent multiple options' reward probabilities and which areas are most important.

We recorded the activity of 16,780 single neurons across the medial frontal cortex (MFC), dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), orbitofrontal cortex (OFC), dorsal premotor cortex (PMd), inferior frontal gyrus (IFG), striatum and amygdala in two monkeys as they performed a reward-based decision making task. Specifically on each trial, subjects choose between two options associated with different probabilities of receiving distinct flavors of fruit juice. To establish how population activity dynamically changes during decision making, we used state-space and linear discriminant analyses to classify the neural activity associated with the reward probability of each of the available options on individual trials, which we refer to as "states". Here we define "states" as patterns of ensemble activity specifically associated with the reward probability of a distinct option.

Following the presentation of the options, neural population activity oscillated between states representing both available options' probabilities before quickly converging towards the option subjects would ultimately choose. Single-area classifiers as well as a neuron dropping analysis revealed that probability-related states were most reliably decoded within ventrolateral PFC and amygdala compared to other areas. Importantly, the neural states that we classified from neural activity were directly related to subjects behavior. Specifically, we found that a greater number



of saccades during the evaluation of the options, indicative of greater hesitancy, was associated with a stronger representation of the unchosen state.

Our findings support the idea that decision-making is a dynamic process, with neural states related to the probability of each option fluctuating as we evaluate them. Our data show that a core set of areas in ventral PFC and amygdala are central to representing probability-related neural states indicating their critical role in this type of decision-making.

**Disclosures:** N. Valluru: None. F.M. Stoll: None. P.H. Rudebeck: None.

## **Poster**

### **PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.08/DD6

**Topic:** I.03. Decision Making

**Support:** Grossman Center for the Statistics of the Mind  
Air Force Office for Scientific Research (21RT0878)  
R01NS113113  
R01MH122513  
Kavli Center, Columbia University

**Title:** Shared and distinct functions of macrocircuit nodes responsible for a perceptual decision

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**Abstract:** The neurobiology of perceptual decision-making offers a valuable window into the neural mechanisms that link sensory input, cognitive evaluation, and motor output. The integration of mathematical theory, quantitative behavior, and both correlational and causal experiments has established a promising framework for understanding interactions within and between brain areas that comprise the larger macrocircuit. Recent advances in neural recording technologies, including Neuropixels probes, now permit (1) simultaneous recordings from functionally connected populations, (2) tracking of neural dynamics over the course of a single decision, and (3) perturbation of one circuit node while recording from others. Here, we report on ongoing work characterizing the functions and interactions of macrocircuit nodes involved in a perceptual decision reported via saccadic eye movement. Prior findings indicate that neurons in the lateral intraparietal area (LIP) encode a drift-diffusion decision variable (DV), while neurons in the deep layers of the superior colliculus (SC) detect threshold crossings in the DV, triggering decision termination via saccadic or non-saccadic bursts. New Neuropixels recordings from SC

and dorsal pulvinar (dPulv) show that these non-saccadic bursts excite dPulv neurons, likely contributing to covert decision termination and cessation of evidence integration in LIP. In contrast to the distinct roles of LIP and SC, new recordings from the frontal eye field (FEF) reveal drift-diffusion dynamics resembling those of LIP. The FEF signal also meets criteria for a decision variable, influencing both choice and response time. The nature and degree of redundancy between FEF and LIP remain to be fully clarified.

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## **Poster**

### **PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.09/DD7

**Topic:** I.03. Decision Making

**Support:** 1RF1NS127122-01

**Title:** Inferring Latent Policies from Behavior via Model-Based Belief Update

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**Abstract:** Natural and artificial agents often act under uncertainty, relying on latent internal representations to guide behavior. In partially observable settings, these representations can be formalized as beliefs—probability distributions over possible world states that evolve according to an agent’s internal model. However, deriving belief dynamics is analytically intractable in complex environments. We introduce a simulation-based algorithm that approximates Bayesian belief updates using only a generative internal model of environment dynamics. We apply this method to a monkey foraging task, in which unconstrained primates navigate a 3-dimensional, naturalistic environment to forage for juice rewards whose availability is signaled by uncertain environmental cues. Our framework infers latent belief trajectories from behavior, revealing that they evolve on a low-dimensional manifold and can be interpreted as the synthesis of behaviorally meaningful, observable variables such as spatial location and reward timing. In a subsequent analysis, we use these inferred belief trajectories to uncover distinct behavioral policies using a hidden Markov model. Each policy is optimized for distinctiveness and low entropy. When applied to simulated data, our method accurately detects policy switches. When applied to real data, our method discovers blocks of time when the monkey behaves differently, and these inferred policies are consistent across different sessions. Overall, our framework offers a principled approach to inferring internal model-based representations and non-stationary

policies, providing a testable foundation for identifying neural correlates of belief-guided behavior.

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## **Poster**

### **PSTR235: Non-Human Primate Neural and Behavioral Processes**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR235.10/DD8

**Topic:** I.03. Decision Making

**Support:** Mathworks Fellowship

**Title:** A framework for investigating sensory integration in marmosets

**Authors:** \*A. B. FATH<sup>1</sup>, G. FENG<sup>2</sup>, W. MENEGAS<sup>1</sup>;

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**Abstract:** Atypical sensory processing has been observed across several neurodevelopmental disorders, yet the behavioral and neural mechanisms underlying this deficit remain poorly understood. More specifically, such sensory deficits have been observed across several sensory modalities and have been especially well documented in humans when perceptual judgments require the accumulation and integration of sensory information over time. The study of sensory alterations in rodent models of neurodevelopmental disorders have produced variable results and are limited in their ability to accurately reflect human conditions and predict outcomes. Non-human primate, marmoset, models of neurodevelopmental disorders, such as autism spectrum disorder (ASD), have recently been developed, which allow for a unique opportunity to better understand the complex behavioral and neural processes underlying sensory processing in neurodevelopmental disorders. In this study, we propose a framework to study sensory processing in marmosets. We implemented a free response version of a pulse based sensory evidence accumulation task originally developed in rats, and use pose estimation along computational models to quantify and understand the process of sensory integration. The task presents sensory information in a sequence of flashes on the left and right sides of a screen, while freely moving marmosets must choose the side with higher flash probability to receive a reward. The task presents a speed-accuracy tradeoff, in which longer response times result in a greater probability of choosing the correct side, as it allows the marmoset to sample more sensory (flash) evidence. We hope this framework will provide a foundation for studying sensory processing deficits across marmoset models of neurodevelopmental disorders in the future.

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## **Poster**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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**Topic:** I.03. Decision Making

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**Title:** Mechanism for the generalization of action syntax in a trained recurrent neural network model

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Cambridge, MA

**Abstract:** A hallmark of higher cognition is the ability to solve novel problems by generalizing previously learned knowledge. However, the neural circuit mechanisms underlying this capability remain poorly understood. To investigate this, we trained monkeys to perform an action syntax task, and a recurrent neural network (RNN) to solve an abstract version of the same task. In this paradigm, subjects are required to trace an image on the screen that contains different shapes using a sequential rule (termed “action syntax”), such as: “first complete all the lines, then all the circles”.

Both monkeys and the RNN were trained using problems with fewer shapes and successfully generalized to more complex problems with more shapes. Dissection of the trained RNN reveals a dynamical mechanism that enables this generalization. First, the RNN's initial state encodes the number of different shapes in orthogonal directions, which we refer to as “repetition directions.” Crucially, this orderly representation extends to novel problems due to the alignment of the input weights with these directions. Second, while drawing a specific shape, population activity evolves along the corresponding repetition direction within a slow manifold. Because these directions are orthogonal, information about the remaining shapes is preserved. Third, upon completing a shape, the network state transitions through a “tunnel” to initiate the next shape's repetition. These tunnels exhibit parallel flow fields, allowing the information of remaining repetitions to persist across transitions.

Neural recordings from the frontal cortical areas showed signatures consistent with this mechanism. Single RNN units encoded the current shape being drawn, its ordinal position in the sequence, and transitions at action boundaries—mirroring observations from prior recordings in action sequencing tasks. Together, these findings propose a neural mechanism by which abstract rules involving repetition and ordering of actions can be implemented and generalized.

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**PSTR235: Non-Human Primate Neural and Behavioral Processes**

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**Topic:** I.03. Decision Making

**Support:** NIH R01 DA047870  
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**Title:** Arbitration through modulations of representation geometry in the prefrontal cortex

**Authors:** \*J. WOO<sup>1</sup>, M. C. WANG<sup>2</sup>, R. BARTOLO<sup>4</sup>, B. B. AVERBECK<sup>5</sup>, A. SOLTANI<sup>3</sup>;  
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**Abstract:** In naturalistic settings, the brain should learn alternative models of how stimuli, their features, and actions predict the outcomes, and arbitrate between these predictive models of the environment. Previous studies in context-dependent perceptual decision making, visual attention, and category learning have shed light on how attentional demands alter the dynamics of neural representations, suggesting that the task-relevance of a variable can modulate both its encoding magnitude as well as its representational geometry. These mechanisms, however, has only been shown for tasks where the relevant attribute is explicitly cued on a trial-by-trial basis. Thus, it is unclear whether and how those mechanisms generalize to internally generated signals learned from reward feedback over many trials. To address this question, we performed high-density recordings of lateral prefrontal cortex (LPFC) activity in monkeys (n=2) performing a probabilistic reversal learning task with the uncertainty about relevant attribute in a given block of trials (stimulus identity vs. action). Using reinforcement learning models, we found evidence of dynamic, competitive interactions between stimulus-based and action-based learning, as well as single-cell and population-level representations of the arbitration weight. Moreover, the arbitration weight systematically modulated both the strength and geometry of value representations. Specifically, the encoding of the values associated with the task-relevant feature was enhanced, and the differential value signals were selectively routed to a choice neural subspace, resulting in stronger alignment between value and choice representations. Both effects were further modulated by the previous trial's reward outcome, highlighting the role of reward feedback in adjusting the animal's arbitration strategies. To determine which of these effects is more critical in controlling behavior, we performed a targeted dimensionality reduction to derive a time-independent encoding subspace for critical task-related variables. We found that the routing of differential value to choice subspace, measuring the alignment between the two subspaces, predicted the arbitration weight on each block better than the strength of differential

value signal. Overall, our results extend previous findings on how specific external cues change representation geometry to alter choice behavior, to situations where animals rely on internally generated signals learned through reinforcement. Moreover, they suggest that reward feedback could provide a mechanism for the observed changes in the population code, enabling flexible behavior.

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## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.01/DD11

**Topic:** H.03. Motivation

**Support:** NIDA R01 DA049837  
NIDA R01 DA056534  
NIDA DA061483

**Title:** Parental Behavior

**Authors:** \*S. KU<sup>1</sup>, G. A. MIRANDA<sup>2</sup>, M. DUPUIS<sup>3</sup>, J. FLOWERS<sup>4</sup>, D. A. BANGASSER<sup>2</sup>;  
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**Abstract:** Stress is a major risk factor for development of postpartum disorders, which can be mimicked using a limited bedding and nesting (LBN) manipulation. LBN dams and pups reside on a metal grate from postnatal day (PND) 2-10 and are compared to animals in standard housing conditions. Previously, we found that LBN increases dam's pup-directed behavior and decreases self-care. To determine if LBN impacts additional postpartum behaviors, we randomly assigned Long Evans dams (100-150 days old) to standard (n = 15) or LBN (n = 12) housing, then ran a resident-intruder task on PND10 with a male intruder to elicit aggression. LBN dams have lower total attack durations ( $p = 0.01$ ), which is driven by significant decreases in pinning ( $p = .009$ ) and wrestling ( $p = .03$ ), specifically. We conducted whole-brain cFos to determine regions underlying these behavioral shifts. LBN dams show decreased cFos in the lateral habenula ( $p = 0.03$ ), which has been strongly implicated in intermale aggression. Importantly, total attack duration is significantly positively correlated with lateral habenula cFos expression  $r(16) = .97, p < .001$ , indicating that this region is involved in maternal defensive behavior. Ongoing work leverages chemogenetics to discern a causal role for lateral habenula in this stress effect and functional connectivity analysis to delineate circuitry involved in maternal aggression.

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**Poster**

**PSTR236: Social Communication and Behavior Across Species**

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**Program #/Poster #:** PSTR236.02/DD12

**Topic:** H.03. Motivation

**Support:** NIH Grant R01HD113522

**Title:** Mesolimbic dopamine signaling mediates increased food motivation and hedonic feeding during lactation in mice

**Authors:** \*T. PATTNAIK, B. WANG, E. BORROWMAN, L. VILLANO, P. SWEENEY;  
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**Abstract:** Lactation represents a critical physiological period that imposes significant energetic demands on mothers and impacts both maternal and offspring health. To meet the demands of milk production and heat generation for their young, lactating mammals substantially increase food intake. However, the underlying behavioral, molecular, and neural mechanisms driving this increased feeding behavior during lactation remain poorly understood.

In this study, we investigated changes in feeding behavior and food motivation in lactating mice using automated home cage feeding devices (Feeding Experimentation Devices; FED3). We also characterized hedonic food intake in lactating mice. Our results show that lactation alters meal patterns, increases food-seeking behavior, and increases hedonic feeding in mice. Given the known role of dopaminergic pathways in regulating food-seeking and hedonic eating, we employed pharmacological, chemogenetic, and imaging techniques to explore changes in mesolimbic dopamine signaling during lactation.

Pharmacological inhibition of dopamine receptors potently reduced meal size and food-seeking behavior in lactating mice, normalizing these behaviors to the levels observed in non-lactating animals. To investigate functional changes in dopamine signaling, we used *in vivo* fiber photometry to measure dopamine release in the nucleus accumbens in non-lactating and lactating mice during feeding. Lactating mice exhibit enhanced dopamine release in response to palatable food consumption and refeeding after fasting compared to non-lactating control mice, suggesting that elevated dopamine levels accompany increased feeding during lactation. Increased dopamine signaling was functionally required for elevated hedonic feeding during lactation as both chemogenetic inhibition of ventral tegmental area (VTA) dopamine neurons or dopamine receptor antagonism in the nucleus accumbens both normalized palatable food intake to the levels of non-lactating animals. Furthermore, chemogenetic inhibition of VTA dopamine neurons reduced motivation to seek food in lactating mice, as measured by a progressive ratio food-seeking task. Collectively, our results demonstrate that lactation enhances both the motivation for food and hedonic feeding behavior, and these changes are mediated by the mesolimbic dopamine system.

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**Poster**

**PSTR236: Social Communication and Behavior Across Species**

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**Program #/Poster #:** PSTR236.03/DD13

**Topic:** H.03. Motivation

**Support:** NIDA Grant R21DA059966  
NIDA Grant R01DA056534

**Title:** Resource scarcity disrupts maternal care and alters gene expression in the basolateral amygdala

**Authors:** \*D. ASPESI<sup>1</sup>, E. P. HARRIS<sup>2</sup>, S. KU<sup>4</sup>, R. CRIST<sup>5</sup>, B. C. REINER<sup>6</sup>, D. A. BANGASSER<sup>3</sup>;

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**Abstract:** Socioeconomic constraints significantly affect maternal caregiving, with lasting consequences for offspring development. Resource scarcity represents a potent environmental stressor that disrupts parenting behavior, particularly through its impact on hormone-sensitive brain regions such as the basolateral amygdala (BLA). Yet, the behavioral and molecular consequences of such environmental constraints on maternal behavior remain insufficiently characterized. In this study, we employed the limited bedding and nesting (LBN) paradigm to model postpartum resource scarcity in rats from postnatal day (PND) 2 to 6. Dams under LBN conditions received minimal nesting material and no enrichment, while control dams were provided full bedding, nesting material, and enrichment. PND 5 was identified as a critical time point for behavioral disruptions. Maternal care was observed for two hours (one during the light phase, one during the dark) and care fragmentation and unpredictability was quantified using behavioral entropy rate analysis. On PND 6, brains were collected, and bulk long-read RNA sequencing was performed on the BLA. Relative to controls, LBN dams showed increased pup-directed behaviors (e.g., nursing, pup-carrying), reduced self-care (e.g., grooming), and spent less time away from the nest. They also displayed higher entropy rates, indicating more fragmented and less predictable behavioral sequences. Transition probability analysis further revealed increased transitions into pup-licking/grooming behavior under LBN. Transcriptomic analysis identified 292 differentially expressed genes in the BLA of LBN dams. Pathway enrichment analyses implicated extracellular matrix remodeling processes linked to synaptic plasticity. Estrogen receptor alpha (ESR1) emerged as a key upstream regulator, suggesting altered steroid hormone signaling in response to resource scarcity. These findings demonstrate that environmental stress reshapes maternal caregiving behavior, with associated molecular



changes in the BLA. This work elucidates a potential mechanism linking early-life stress to caregiving variability and developmental outcomes in offspring.

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## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR236.04/DD14

**Topic:** H.03. Motivation

**Support:** Brain & Behavior Foundation NARSAD Young Investigator Award  
BGSU's Department of Psychology Diversity & Inclusion Research Funds

**Title:** Effects of phthalate exposure on maternal neuroanatomy and microglia morphology in Long Evans dams

**Authors:** \***E. SHULTZ**<sup>1</sup>, V. R. RIESGO<sup>1</sup>, S. LAMANCUSA<sup>1</sup>, E. P. SELLINGER<sup>2</sup>, J. WILLING<sup>1</sup>;

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**Abstract:** Phthalates are a class of endocrine-disrupting compounds primarily used to increase the durability and flexibility of plastics. Previous work (Kougias et al. 2018; Riesgo et al 2024) has demonstrated that perinatal exposure to an environmentally relevant mixture of phthalates decreases neurons in the medial prefrontal cortex (mPFC) as well as mPFC volume. Much of the previous literature on phthalates takes a developmental focus on exposed offspring, but mothers themselves are also vulnerable. Phthalates have been shown to alter maternal behavior (Adam et al., 2022) and can interact with immune function resulting in negative reproductive effects (Riesgo et al., 2024). The present study seeks to elucidate the effects of phthalates on the maternal brain by examining mPFC cortical thickness, white matter volume, and microglia density and morphology. Pregnant dams were randomly placed into one of two conditions: phthalate exposure (0.20 mg/kg/day or 1 mg/kg/day onto half of a vanilla cookie) or control (oil). For each group, the percentage of dams giving birth, number of pups per litter born alive, and the sex ratio within litters were assessed. Following weaning of their offspring, dams were sacrificed and their brains fixed and stained for immunohistochemical analysis. MPFC and hippocampal sections were Nissl stained with methylene blue-azure II and alternate sections were stained with IBA-1. Maternal brain weight, mPFC volume, white matter under the PFC, total microglia count, and the ratio of different microglial activation states were examined. This study has important implications for maternal health, particularly for individuals from marginalized backgrounds and low socioeconomic areas who are more likely to be exposed to higher concentrations of environmental toxicants.

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**Poster**

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**Program #/Poster #:** PSTR236.05/DD15

**Topic:** H.03. Motivation

**Support:** NIDA R01 DA049837  
NIDA R01 DA056534  
NIDA DA061483

**Title:** Assessing Postpartum Motivation for Pups vs Female Conspecific Using a Social Operant Paradigm in Long-Evans Rats

**Authors:** \*J. NYAKOA<sup>1</sup>, S. KU<sup>2</sup>, D. A. BANGASSER<sup>1</sup>;

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**Abstract:** Operant behavioral assays are a standardized method to quantify motivation in rodents in laboratory settings. Social operant paradigms, whereby animals press a lever for a social interaction, have allowed for specific and translatable quantification of social motivation. Although these procedures are becoming more widely adopted to assess motivation for same-sex, same-age conspecifics, there is still a paucity of data using these procedures to test motivation across the reproductive periods. This project investigates postpartum motivation for pups vs. a female conspecific by adopting this social operant paradigm to the postpartum period in Long-Evans rats. To this end, we made minor modifications to the barrier for the standard rat social operant Med Associates chambers to retain pups on their side of the chamber. We predicted that dams in the postpartum period would be more motivated for their pups than an adult female target. For training, before pregnancy, virgin females were trained to associate a lever press (on the sucrose lever) with a sucrose reward to familiarize them with the chambers and that lever pressing leads to a reward. On postnatal day (PND) 11, when pups can thermoregulate, postpartum dams were placed in a social operant task and trained to press the social lever (distinct from the sucrose lever) for a social interaction with their pups or an adult female conspecific. After 3 days of training on a fixed ratio schedule, rats were trained on a progressive ratio schedule to discern social motivation for pups or conspecifics. The following day, they were presented with a choice between a sucrose and social reward. Preliminary data indicate that postpartum dams press significantly more for their pups (n=5) than a control female conspecific (n=4, p = .03). Pup-pressing was further associated with a higher breakpoint during a progressive ratio assessment than conspecific, indicating increased postpartum motivation for pups. During choice, dams pressing for their pups show a stronger preference for a social interaction, while dams pressing for a conspecific prefer sucrose. Collectively, these findings

indicate that the postpartum period is associated with profound changes in social motivation, and that this motivation is especially directed towards pups. This protocol is a novel implementation of established operant assays at a critical reproductive time point. Future studies will use this protocol to examine the impact of stress on postpartum motivation and identify brain regions responsible for shifts in maternal motivation.

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## **Poster**

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**Program #/Poster #:** PSTR236.06/DD16

**Topic:** H.03. Motivation

**Support:** Goldstein Pilot Grant  
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**Title:** Care seeking behaviors are modulated by social cues and environments in rodent pups

**Authors:** J. MENDOZA<sup>1,2</sup>, \*K. SHIRAZI<sup>3,2</sup>, K. KON<sup>1,3,4,2</sup>, R. FEJFER<sup>1</sup>, T. KARIGO<sup>1,3</sup>;  
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**Abstract:** Care-seeking behaviors are critical for early survival and shaped by both innate drives and environmental cues. In rodents, these include ultrasonic vocalizations (USVs) and exploratory behavior, often triggered by isolation from caregivers. These responses emerge shortly after birth, peak around postnatal day 7-9 (P7-9), and decline with age. At this stage, olfaction serves as the dominant sensory modality, as visual and auditory systems remain underdeveloped. However, it remains largely unknown how olfactory social cues and social experiences modulate care-seeking behavior and what neural circuitry underlies this modulation. To investigate how social context and rearing conditions influence care-seeking, isolated mouse pups were evaluated in arenas with binary bedding combinations: home cage, unfamiliar female cage, unfamiliar male cage, or clean new cage. Soiled bedding was used because it provided naturalistic olfactory signals. Swiss Webster pups of both sexes were tested at P7-9 and P14-15, raised either by the dam or by both parents. USVs were recorded using high-frequency microphones, and behavior was tracked via machine learning-based pose estimation. A clear preference for home bedding was observed in both age groups and rearing conditions. Dam-reared pups showed reduced USVs and strong avoidance in response to unfamiliar male cues, while biparentally reared pups did not show this decrease in vocalizations and exhibited less avoidance of the male cues. These findings suggest that early social experiences modulate

behavioral responses to unfamiliar olfactory social cues. We are currently investigating the neural circuits that support care-seeking behaviors. By combining behavioral assays with neural circuit dissection, this study lays the groundwork for uncovering how early life experiences influence developing social circuits, offering insight into how social context shapes behaviors critical for survival.

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## **Poster**

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**Program #/Poster #:** PSTR236.07/EE1

**Topic:** H.03. Motivation

**Title:** Oxytocin administration ameliorates social preference impairment caused by maternal separation

**Authors:** \*N. MATSUMOTO<sup>1</sup>, R. NISHIBORI<sup>2</sup>, Y. KINOSHITA<sup>2</sup>, H. NAKAGAWA<sup>2</sup>, K. SHIN'YA<sup>2</sup>, Y. ITO<sup>2</sup>, K. I. KOBAYASHI<sup>2</sup>;

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**Abstract:** Excessive early-life stress significantly increases the risk of developing psychiatric disorders and social behavioral abnormalities later in life. Maternal separation (MS), where pups are temporarily isolated from their mothers, is often used in rodent studies as an early-life stress model. Notably, adult Mongolian gerbils (*Meriones unguiculatus*) subjected to MS exhibit an impaired ability to form social bonds with novel conspecifics. Oxytocin (OXT), a neuropeptide has recently been linked to social behavioral disorder through dysfunction of OXT system. In the present study, we investigated the involvement of OXT in MS-induced social behavioral abnormalities. More specifically, to investigate whether reduced OXT levels or sensitivity contribute to MS-induced abnormalities, we experimentally assessed the efficacy of OXT administration in alleviating these deficits. Gerbils were subjected to MS for 24 hours from postnatal day 7 to day 8. At 3 months of age, they underwent a social preference test followed by a social novelty test. In the social preference test, gerbils were simultaneously presented with a conspecific of the same sex (social stimulus) and an empty box of comparable size, each placed in a separate mesh cage. Time spent near each stimulus was measured. Results revealed that MS gerbils administrated saline (0.1 mL) as control injection exhibited no significant preference for social stimulus. In contrast, both normally reared animals administrated saline and MS gerbils administered OXT (0.1 mg/kg in 0.1 mL saline) showed significant preference for the social stimulus. In the subsequent social novelty test, the animals were simultaneously presented with the previously introduced conspecific (familiar social stimulus) and a novel conspecific (novel social stimulus). No significant stimulus preference was observed in any group, and time spent

near each stimulus was comparable among different groups. These results indicate that MS disrupts the preference for social over non-social stimulus, and that OXT administration ameliorates this impairment. Additionally, because OXT administration neither enhanced nor diminished the preference for the novel social stimulus over the familiar social one, it is suggested that OXT administration does not disrupt social preference itself. Our findings suggest that impaired social bonding in MS animals may be partly due to altered preference for social stimuli, and that this alteration is potentially attributable to decreased OXT levels and/or reduced sensitivity. We will discuss how the number of hypothalamic OXT-producing cells is related to these symptoms.

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## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.09/Web Only

**Topic:** H.03. Motivation

**Title:** The impact of sex and familiarity on social motivation in Alston's singing mouse

**Authors:** \*B. MARDIS<sup>1</sup>, S. M. PHELPS<sup>2</sup>;

<sup>1</sup>Interdisciplinary Neurosci. Program, <sup>2</sup>Integrative Biol., Univ. of Texas at Austin, Austin, TX

**Abstract:** Sex differences in social motivation are thought to play an important role for sex differences in mental health, but most animal models of sex differences focus on behaviors specific to only one sex, rather than differences in degree. To address this gap, we use the advertisement vocalizations of Alston's singing mouse (*Scotinomys teguina*) as a model of sexually dimorphic but continuous differences in social motivation. Male *S. teguina* vocalize more often than females and engage in back-and-forth vocal exchanges with sub-second latencies. Previous work suggests these 'conversations' may play a role in negotiating space use and access to resources, but it is unknown whether females use song for the same purposes. In this study, we examine whether familiarity with a vocal partner influences social motivation and how sex may modulate this relationship. Adult singing mice (n= 16 males, 16 females) were co-housed from weaning with a same-sex littermate. We then obtained audio recordings of same-sex pairs of mice in adjacent recording chambers, allowing auditory and olfactory cues to travel, but preventing visual or tactile contact. Pairs were either familiar (cage-mates) or unfamiliar (from different cages). Subjects were run in counterbalanced blocks of 8 mice (2 male pairs, 2 female pairs), with each mouse recorded in both the unfamiliar and familiar conditions. We found that individuals produce more songs when paired with an unfamiliar mouse, supporting the hypothesis that song is primarily used to advertise to novel individuals and negotiate access to space or resources. This effect was consistent across both sexes. For a subset of mice (n = 3 males, 3 females), we also recorded their vocal response to audio playback of a familiar (cage-

mate) vs. unfamiliar mouse's song, to explore whether they recognize their familiar partner in the absence of olfactory cues. Though this follow-up is underpowered, the results suggest a trend in which mice sing more in response to a familiar playback. This discrepancy in the direction of the familiarity effect from live counter-singing to playback suggests that the vocal effort of a partner may modulate the impact of familiarity on song production. Additionally, our experiment revealed a high degree of asymmetry in the song rate of sibling pairs, which may indicate the formation of dominance relationships where the subordinate mouse suppresses its song output. This work reveals key details about how *S. teguina* utilize their vocalizations and enables future research investigating the neural mechanisms that underlie these behavioral phenomena.

**Disclosures:** **B. Mardis:** None. **S.M. Phelps:** None.

## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.10/EE3

**Topic:** H.03. Motivation

**Support:** NIH Grant 5K08NS105938 (to N.A.F)  
SFARI Bridge to Independence award (to N.A.F)  
generous donation from Edward Elliott

**Title:** Medial prefrontal ensemble activity underlying context-dependent social decision-making is disrupted in mice lacking SHANK3

**Authors:** \***D. KWAK**<sup>1,2</sup>, B. C. CURD<sup>1</sup>, N. A. FROST<sup>1</sup>;  
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**Abstract:** Adaptive decision-making in response to dynamic environmental and social contexts is critical for the survival of an organism. The medial prefrontal cortex (mPFC) regulates flexible decision-making during complex behaviors, including social interactions, which allows context-dependent optimization of behavioral outcomes. We have recently demonstrated that the mPFC encodes persistent representations of social information in parallel with representations of the environment. However, it is not well understood how changes in context might alter decisions to initiate social interactions or how they are represented in the mPFC. Moreover, while we have previously demonstrated that mice lacking autism-risk gene *SHANK3* have abnormal recruitment of prefrontal activity during social interactions, it is not known how *SHANK3* might affect the encoding of behavioral decisions during social interaction. In this study, we sought to characterize how social behaviors are shaped by context and the underlying neuronal ensemble activities that modulate decisions of such behaviors. We utilized microendoscopic calcium imaging in freely moving mice to record the mPFC neuronal activity during social situations, which varied by context with different motivational drives. We show that the proactive initiation of social interaction and the persistence of social behavioral state are heavily influenced by

context, and this context-dependent motivation is lost in mice lacking *SHANK3*. Underlying this impaired motivational drive, we observe calcium dynamics underlying active decision making to initiate social interactions are present in wildtype mice, but lost in littermates lacking *SHANK3*. These results suggest that mPFC activity underlies context-dependent social interactions, which are lost in a mouse model of autism.

**Disclosures:** D. Kwak: None. B.C. Curd: None. N.A. Frost: None.

## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.11/EE4

**Topic:** H.03. Motivation

**Support:** T32MH087004  
BBRF (PI:Dai)

**Title:** Investigating Synaptic and Neural Mechanisms of Cbln2 in Social Behavior

**Authors:** \*D. T. LEWIS-SANDERS<sup>1</sup>, J. DAI<sup>2</sup>;

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**Abstract:** Disruption of synaptic cell-adhesion molecules—including neurexins (Nrxns), cerebellins (Cblns), and glutamate delta-type receptors (GluDs)—has been implicated in the social deficits commonly observed in neuropsychiatric disorders such as autism spectrum disorder (ASD) and schizophrenia. However, the precise mechanisms underlying these deficits, particularly the brain regions and synaptic changes involved, remain poorly understood. Cbln2, a secreted synaptic organizer, forms a trans-synaptic complex with presynaptic Nrxns and postsynaptic GluDs, modulating behaviors related to social interaction, emotional regulation, and compulsivity. Using a conditional knockout (cKO) reporter mouse model, we observed strong expression of Cbln2 in the hippocampal ventral subiculum (vSub)—a region critically involved in socio-affective processing. AAV-Cre-mediated deletion of Cbln2 in the vSub led to reduced social preference in the three-chamber social interaction test, as evidenced by a decreased Social Index (SI) ratio. We hypothesize that Cbln2 downregulation in vSub neurons induces social deficits by promoting the accumulation of GluA2-lacking, calcium-permeable AMPA receptors (CP-AMPA) at downstream synapses. Our initial data support this model, indicating that Cbln2 regulates CP-AMPA expression and may thus contribute to synaptic dysfunction underlying social impairments. To identify downstream targets of vSub Cbln2<sup>+</sup> neurons, we injected AAV-DJ-hSyn-tdTomato into the vSub and found robust projections to the nucleus accumbens (NAc) and lateral septum (LS). To probe circuit-specific mechanisms, we will inject AAV2-retro-hSyn-FlpO into the NAc or LS and a Cre-dependent viral vector (AAV-EF1a-fDIO-Cre) into the vSub of Cbln2 cKO mice. This study aims to define the role of Cbln2 in regulating

glutamate receptor composition at synapses and its impact on social behavior. Our findings are expected to provide mechanistic insight into CP-AMPA-mediated synaptic transmission and its contribution to social dysfunction, with the potential to inform new therapeutic strategies for autistic behaviors and neuropsychiatric disorders.

**Disclosures:** D.T. Lewis-Sanders: None. J. Dai: None.

## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.12/EE5

**Topic:** H.03. Motivation

**Support:** NIMH Grant 1RM1MH138313-01

**Title:** Systematic Analysis of Individual and Social Behaviors Across Genetic Models of Neurodevelopmental Disorders

**Authors:** \*K. B. MCCULLOUGH<sup>1</sup>, H. GABEL<sup>2</sup>, H. OVIEDO<sup>1</sup>, A. V. KRAVITZ<sup>3</sup>, J. D. DOUGHERTY<sup>1</sup>, S. E. MALONEY<sup>4</sup>;

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<sup>4</sup>Psychiatry, WashU Med., St. Louis, MO

**Abstract:** Over the past decade, there has been a marked increase in the study of genetic associations underlying neurodevelopmental and psychiatric disorders (NPDs). Despite this progress, systematic investigations into how these genetic liabilities affect behavioral phenotypes remain limited. Among the core domains of impairment in NPDs, social dysfunction represents both a defining characteristic and a compelling area of study for researchers and affected communities alike. To address this gap, the Washington University Scalable Mouse Assay Center (WU-SMAC) was established with the goal of systematically assessing behavioral outcomes across 100 NPD-associated genes over a five-year period. We examined the impact of genetic liability on both individual and social behavioral outcomes across multiple mouse models harboring mutations in genes implicated in NPDs, including *Myt1l*, *Dnmt3a*, *Wac*, *Nf1*, *Shank3b*, *Cdkl5*, *Cntnap2*, *Fmr1*, and *Znf292*. We employed a full-contact dyadic social interaction assay. Heterozygous and homozygous mutant mice, aged 8-16 weeks, along with wild-type littermates, were paired with age-, sex-, and strain-matched stimulus animals. Each mouse was first habituated to the arena to allow for quantification of individual behaviors—such as exploratory activity and repetitive behaviors (e.g., jumping, excessive grooming). Following the habituation of both animals, the dyad was introduced and recorded for an additional 10 minutes to assess social interaction. While full-contact dyadic interaction provides an ethologically relevant assay for evaluating social behaviors, manual scoring is labor-intensive, subjective, and limited in its sensitivity to subtle behavioral differences. To address these challenges, we implemented open-



source deep learning models to automate behavioral analysis. Pose estimation was performed using a neural network across hundreds of thousands of video frames with minimal experimenter input, followed by supervised classification using a random forest model trained on experimenter-annotated behaviors. This pipeline enables high-throughput, unbiased, and reproducible quantification of both individual and social behaviors. The impact of these distinct mutations on sniffing behavior, including duration and frequency, among other social behaviors were analyzed across several models, including those carrying mutations in *Myt1l*, *Dnmt3a*, *Wac*, *Nf1*, *Shank3b*, *Cdkl5*, *Cntnap2*, *Fmr1*, and *Znf292*. These findings highlight the utility of automated, high-resolution behavioral phenotyping in uncovering gene-specific contributions to social and repetitive behaviors.

**Disclosures:** K.B. McCullough: None. H. Gabel: None. H. Oviedo: None. A.V. Kravitz: None. J.D. Dougherty: None. S.E. Maloney: None.

## Poster

### PSTR236: Social Communication and Behavior Across Species

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.13/EE6

**Topic:** H.03. Motivation

**Support:** STI2030-Major Projects (2021ZD0203000 (2021ZD0203002))  
National Science Foundation of China (32171016)  
Tsinghua University Dushi Program  
Leon Levy Neuroscience Fellowship (to K.L.)

**Title:** Cortico-hypothalamic mechanisms of integrating internal states with social information to control sociosexual interest

**Authors:** \*X. SONG<sup>1,2,3</sup>, Y. WANG<sup>1,2</sup>, Y. ZHOU<sup>1,2</sup>, J. MA<sup>1,2,3</sup>, F. ZHANG<sup>1,2</sup>, L. WEI<sup>1,2,3</sup>, Y. CHEN<sup>1,2</sup>, Y. HAN<sup>1,2,3</sup>, K. LI<sup>1,2,3</sup>;

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**Abstract:** In the extensive evolutionary trajectory of humans and animals, sociosexual interest between the sexes have consistently constituted a core mechanism underpinning species reproduction and survival. For female mammals, their estrus cycle can modulate sociosexual interest to elicit sexual behaviors suggesting cognitive involvement. The medial prefrontal cortex (mPFC) regulates high-order social cognition; whether mPFC integrates social information with estrous states to exert top-down control of sociosexual interest remains unknown. Here we found *Cacna1h*-expressing neurons (mPFC<sup>Cacna1h+</sup>) are the primary estrous-status tracker in mPFC. Inhibiting mPFC<sup>Cacna1h+</sup> neurons or projections in anterior hypothalamic nucleus (AHN) robustly attenuated sociosexual interest in estrous females whereas heightened in males. Miniscope imaging reveals that mPFC<sup>Cacna1h+</sup> neurons encoded sociosexual interest more strongly during

estrus and represented self-estrous status and self-sex. Mechanistically, periodic upregulation of *Cacna1h* encoded sufficient T-type-calcium channels that drove estrus-specific activity patterns and mediated sexual dimorphism in mPFC<sup>Cacna1h<sup>+</sup></sup> neurons. Overall, we identify estrus-tracking neurons in mPFC that concurrently encode sociosexual interest and represent self-states to drive sociosexual interest through hypothalamic outputs based on estrous-state changes and sexes. For males, their sexual experience is known to facilitate male mating behaviors; however, neural mechanisms encoding sexual experience in males remain elusive. Combining multimodal behavioral analysis techniques, we discovered that sexually experienced males exhibit distinct "deep social state" compared to the "shallow social state" of sexually naïve males. mPFC *Cacna1h* dysfunction in sexually naïve male mice induces a sociosexual interest and state resembling that of sexually experienced males. Notably, sociosexual interaction of sexually naïve males triggered more Fos<sup>+</sup> neurons in the lateral preoptic area (LPO), a key hypothalamic output of mPFC<sup>Cacna1h<sup>+</sup></sup> neurons. Using the FosTRAP system, we labeled LPO neurons (LPO<sup>TRAPed</sup>) activated during sociosexual interaction in naïve males, and bidirectional modulation of these neurons switched social states between sexual experienced and naïve males. In conclusion, our findings uncover a cortico-hypothalamic mechanism that integrates internal states and social cues to exert sexually bivalent control of sociosexual interest.

**Disclosures:** X. Song: None. Y. Wang: None. Y. Zhou: None. J. Ma: None. F. zhang: None. L. Wei: None. Y. Chen: None. Y. Han: None. K. Li: None.

## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.14/EE7

**Topic:** H.03. Motivation

**Support:** NIH Grant R01MH129641

**Title:** Mapping Individual Social Variation and Intra-Group Dynamics Across Social Separation and Reunion

**Authors:** O. TIMMERMANS<sup>1</sup>, \*J. MCHENRY<sup>2</sup>, E. BLAINE<sup>1</sup>;

<sup>1</sup>Duke Univ., Durham, NC, ; <sup>2</sup>Psychology & Neuroscience, Neurobio., Duke Univ., Durham, NC

**Abstract:** Complex prosocial and antagonistic dynamics emerge within and between social groups, yet individual variability and intra-group shifts during social disruption remain poorly quantified—largely due to prior limitations in multi-animal tracking and behavioral analysis. Here, we leverage Social LEAP Estimates Animal Poses (SLEAP), a deep learning-based tracking platform, to quantify individual- and group-level social interactions in adult mice over time. This approach enables high-resolution analysis of the stability and selectivity of social relationships during group housing and after experimentally imposed social separation. By extracting fine-resolution temporal and spatial features of physical contact alongside diverse

subtypes of prosocial and antagonistic behavior, we reveal robust and stable differences in social regulation across individuals and groups. Notably, we observe strong dyadic selectivity and temporal persistence of social preferences within groups. Complementary neural analyses implicate dynamic recruitment of hypothalamic social regulatory ensembles in shaping these behavioral responses. Ongoing work aims to further resolve the neural substrates of distinct social states and to identify how specific individuals influence broader group dynamics, both during routine interactions and following social disruption. Together, these findings highlight the complexity, selectivity, and stability of innate social behavior, and show how perturbations amplify individual differences and reveal the roles of key individuals in maintaining group structure.

**Disclosures: J. McHenry:** None.

## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.15/EE8

**Topic:** H.03. Motivation

**Support:** NIH Grant MH137204

**Title:** Astrocyte activity in the paraventricular nucleus of thalamus modulates neuronal function and social behavior via GLT1-mediated glutamatergic signaling

**Authors:** \*A. BENNETT<sup>1</sup>, H. KIM<sup>1</sup>, J. LEE<sup>2</sup>, S. CHO<sup>3</sup>, S. KANG<sup>1</sup>;

<sup>1</sup>Pharmacol. and Toxicology, Med. Col. of Georgia at Augusta Univ., Augusta, GA; <sup>2</sup>Dept. of Biomed. Engin., Hanyang University, Col. of Med., Seoul, Korea, Republic of; <sup>3</sup>NMR-MRI(S), Natl. High Magnetic Field Lab., Tallahassee, FL

**Abstract:** Social behavior is essential for animals to maintain healthy patterns of life, and disruptions in these behaviors are associated with various psychiatric and neurological conditions. The paraventricular nucleus of the thalamus (PVT) has emerged as a key brain region involved in encoding contextual salience and aversion, including the regulation of social behaviors. Recent evidence indicates that PVT neuronal activity is tightly linked to social context and significantly correlates with social behavior dynamics. While astrocytes have traditionally been seen as structural support cells, evidence suggests they play a role in neural circuit function by forming tripartite synapses with neurons and modulate neuronal activity through gliotransmitter release or neurotransmitter uptake. However, how astrocytes and neurons in the PVT function together to regulate social behaviors remains unclear. To address this, we chemogenetically activated astrocytes in the PVT by expressing hM3Dq DREADDs under the GFAP promoter. First, we validated astrocytic activation using GCaMP8s calcium imaging, confirming increased calcium transients following activation. We then assessed the impact on neuronal function using in-vivo and ex-vivo electrophysiological approaches. Chemogenetic

activation of PVT astrocytes significantly increased local neuronal firing rates. However, simultaneous in-vivo recordings of local field potentials across PVT-associated brain regions, including the medial prefrontal cortex (mPFC), nucleus accumbens (NAc), amygdala, and ventral hippocampus, revealed a reduction in theta-frequency coherence with the PVT. In ex-vivo experiments, astrocyte activation enhanced evoked excitatory postsynaptic currents (eEPSCs) in nearby PVT neurons. Notably, this enhancement was blocked by DHK, a selective inhibitor of GLT1 (also known as EAAT2/slc1a2), implicating astrocyte-mediated glutamate uptake in modulating neuronal synaptic activity. Behaviorally, activation of PVT astrocytes impaired social recognition in a three-chamber social interaction task. Mice showed reduced preference for social novelty. Importantly, selective deletion of GLT1 in PVT astrocytes reproduced these behavioral deficits, mirroring the effects of astrocyte activation. In summary, our findings demonstrate that astrocytes in the PVT regulate adjacent neuronal activity by directly modulating glutamatergic signaling via GLT1. This astrocyte-neuron interaction plays a crucial role in shaping social behavior, highlighting astrocytic glutamate regulation as a potential therapeutic target for disorders characterized by social deficits.

**Disclosures:** A. Bennett: None. H. Kim: None. J. Lee: None. S. Cho: None. S. Kang: None.

## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.16/FF1

**Topic:** H.03. Motivation

**Support:** NIH Grant R01GM148960  
NIH Grant P20GM125508

**Title:** Hyper neural activities in the brain are associated with asociality and repetitive circling in the Mexican cavefish

**Authors:** \*M. HASEGAWA<sup>1</sup>, V. LIMA FERNANDES<sup>3</sup>, M. PUGH DE LOS REYES<sup>4</sup>, E. STEVENSON<sup>1</sup>, M. IWASHITA<sup>2</sup>, M. YOSHIZAWA<sup>2</sup>;

<sup>2</sup>Sch. of Life Sci., <sup>1</sup>Univ. of Hawaii at Manoa, Honolulu, HI; <sup>3</sup>Inst. de Biologie Valrose, Univ. Côte d'Azur, Nice, France; <sup>4</sup>USC, Los Angeles, CA

**Abstract:** Most known cave animals are asocial and have adapted to cave habitats in a relatively short amount of time. These asocial species are thought to have impaired social decision-making neural networks due to disuse. Cavefish show dysregulated gene expression in neural genes, exhibiting a large overlap in the same directional expression changes (up or down regulations) seen in the brains of patients with autism (>58.5% of 3,152 cavefish orthologs). These analyses for differentially expressed genes in cavefish and humans indicated the shared dysregulation of the dopaminergic and GABAergic systems. Despite gene dysregulation and potential neural network impairment, recent studies by our team and our collaborators suggested that sociality is

promoted through ketosis (via fasting, ketogenic diet, or ketone body supplementation) in both asocial cavefish and patients with autism. However, the mechanism of how ketosis improves sociality is largely unknown. In this study, we identified the brain-wide hyper neural activity in cavefish. By using a modified CUBIC and LIMPID brain clearing method and immediate early gene (phosphorylated ERK: pERK) labeling, we revealed that cavefish showed neural activities in the social decision-making center (SDMC: POA, striatum, and nucleus accumbens) comparable to those of surface fish but showed hyper neural activities in other brain areas (telencephalon, hypothalamus, cerebellum, and hindbrain). Ketogenic diet feeding reduced these hyper activities in cerebellum and hindbrain while keeping activities at SDMC, indicating that the ketogenic diet increases the S/N ratio at SDMC. This study will provide new insight into the asocial brain condition and how it is associated with metabolic ketosis, hinting at the social retrieval under a genetically asocial condition.

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## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.17/FF2

**Topic:** H.03. Motivation

**Support:** Howard Hughes Medical Institute

**Title:** Distinct social behavioral functions of P1 neuronal subtypes in male fruit flies

**Authors:** G. M. RUBIN<sup>1</sup>, C. MANAGAN<sup>2</sup>, S. G. MILLER<sup>3</sup>, K. BOONE<sup>4</sup>, C. MORROW<sup>2</sup>, A. A. ROBIE<sup>5</sup>, A. L. TAYLOR<sup>6</sup>, K. M. BRANSON<sup>7</sup>, C. SCHRETTER<sup>8</sup>, A. OTOPALIK<sup>3</sup>;

<sup>1</sup>Howard Hughes Med. Inst. Janelia Res. C, Ashburn, VA; <sup>2</sup>HHMI Janelia Res. Campus, Ashburn, VA; <sup>4</sup>Biol., <sup>3</sup>Janelia Res. Campus, Ashburn, VA; <sup>5</sup>Howard Hughes Med. Inst., Ashburn, VA; <sup>6</sup>HHMI Janelia, Ashburn, VA; <sup>7</sup>HHMI Janelia Farm Res. Campus, Ashburn, VA; <sup>8</sup>Janelia Res. Campus - HHMI, Ashburn, VA

**Abstract:** During social interactions, animals rapidly translate multisensory cues into behavioral sequences. In *Drosophila melanogaster* males, a dozen P1a neurons per brain hemisphere have been implicated in the integration of conspecific sensory cues and the gating of aggressive and courtship behaviors. Yet, the neuronal and circuit mechanisms by which the P1a population integrates these sensory inputs and sculpts ongoing behavior remain unknown. Moreover, P1a neurons comprise only a small subset of a broader sexually dimorphic pC1 lineage, for which behavioral and physiological function have not been investigated in detail. In an initial effort to comprehensively characterize the male pC1 population, we leveraged the forthcoming male *Drosophila melanogaster* whole-brain connectome to identify 148 P1 neurons, of which there are 19 subtypes based on morphology and synaptic connectivity. We generated over 100 genetic

driver lines that tile most of these subtypes and executed a battery of social behavioral assays with optogenetic perturbations. Here, we present a collection of P1 subtype-specific genetic driver lines, their morphologies and heterogeneous connectivity patterns, and their distinctive social behavioral phenotypes.

**Disclosures:** G.M. Rubin: None. C. Managan: None. S.G. Miller: None. K. Boone: None. C. Morrow: None. A.A. Robie: None. A.L. Taylor: None. K.M. Branson: None. C. Schretter: None. A. Otopalik: None.

## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.18/FF3

**Topic:** H.03. Motivation

**Support:** NIMH (RO1-MH133123)

**Title:** Cortical dopamine signaling modulates partner-seeking behavior in the socially monogamous prairie vole (*Microtus ochrogaster*) during social loss.

**Authors:** \*C. S. LOWE;  
Pharmacol. and Toxicology, The Univ. of Kansas, Lawrence, KS

**Abstract:** Grief often involves a sense of “yearning” for a lost loved one, which can disrupt daily activities. Recent research looking at receptor expression and behavioral differences in the loss state suggests this preoccupation may be driven by hyperactivity of dopamine signaling in the anterior cingulate cortex (ACC) and insular cortex (IC). This hypothesis was explored here using the socially monogamous prairie vole (*Microtus ochrogaster*) and pharmacological manipulation. Male voles were paired with an opposite-sex partner for one week, and bond status was assessed via a partner preference test (PPT), resulting in three groups: non-bonded loss, pair-bonded intact, and pair-bonded loss. One week later, subjects underwent an odor preference test (OPT) for partner vs. food scented bedding. Prior to OPT, voles were bilaterally and site-specifically infused with vehicle, nonspecific dopamine antagonist, or specific dopamine receptor antagonist targeting the ACC or IC. Time spent in proximity and actively investigating scented bedding was analyzed. Results showed that pair-bonded loss animals spent significantly more time investigating partner odor compared to non-bonded loss and pair-bonded intact controls. Antagonism of dopamine receptors in these cortical structures eliminated this difference, significantly reducing partner odor investigation in pair-bonded loss males to control levels. This is the first study to demonstrate a causal link between dopamine signaling in the ACC and IC and increased partner-associated cue seeking during partner loss. Future research is needed to explore the molecular mechanisms behind this apparent dopamine signaling dysfunction in the loss state.

**Disclosures:** C.S. Lowe: None.

**Poster**

**PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.19/FF4

**Topic:** H.03. Motivation

**Support:** NIMH R01MH133123  
NIDA DA050908, DA056804  
University Graduate Fellowship, First Year Fellowship, University of Kansas

**Title:** Behavioral characterization of conditioned place preference and partner preference formation in a prairie vole (*Microtus ochrogaster*) model of acute heroin withdrawal

**Authors:** \*A. H. TBABA<sup>1</sup>, Z. WANG<sup>2</sup>, A. S. SMITH<sup>3</sup>;  
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**Abstract:** Opioid addiction negatively impacts social relationships as well as an individual's display of context-appropriate social behaviors and social commitments. Opioid-induced deficits in social behaviors have been well-documented in laboratory rodent models, but these models have not been extended to social attachments in adulthood, e.g., pair bonding. Prairie voles (*Microtus ochrogaster*) readily form enduring socially monogamous bonds with mating partners (termed "pair bonds"), characterized by a social preference for affiliation with the partner over novel mating partners. This study aims to assess conditioned place preference (CPP) formation, partner preference formation, and relevant behaviors in male prairie voles at 24 and 48-hrs of heroin withdrawal, respectively. Male prairie voles (n=32) were IP injected with heroin (1.5 mg/kg or 2.5 mg/kg) or vehicle (saline) in a 10-day unbiased CPP paradigm. A separate cohort of 24 males were IP injected with heroin (1.5 mg/kg or 2.5 mg/kg) or vehicle for four days before 24-hour cohabitation with an opposite-sex conspecific (the partner) and subsequent partner preference testing (PPT), where subjects were placed in a three-chamber arena and given access to the partner or a sexually receptive female stranger. Subjects given the 2.5 mg/kg dose spent significantly more time in the drug-associated chamber (p=0.0002, ANOVA, Tukey-Kramer adjustment), while 1.5 mg/kg and vehicle animals showed no specific preference. Additionally, subjects given heroin at 2.5 and 1.5 mg/kg showed no significant difference in time spent engaging in partner- vs. stranger-directed close stationary contact (CSC) compared to controls, who spent significantly more time engaging in partner-directed CSC compared to stranger-directed CSC (p = 0.0061, Kruskal-Wallis). These results confirm that male prairie voles show hedonic response to heroin administration. Furthermore, pair bonding behaviors were impaired after heroin administration, suggesting that neurobiological substrates involved in the formation of socially monogamous bonds may be altered by heroin exposure. Current work examines possible changes in gene expression associated with heroin exposure in the anterior cingulate cortex, a region known to be involved in both pair bonding and spontaneous opioid withdrawal.

**Disclosures:** A.H. Tbara: None. Z. Wang: None. A.S. Smith: None.

**Poster**

**PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.20/FF5

**Topic:** H.03. Motivation

**Support:** NIH grant R01MH125408

**Title:** Social Isolation Induces Motivational Anhedonia in Male Prairie Voles

**Authors:** \*A. ERBACHER<sup>1,2</sup>, F. DUCLOT<sup>1,2</sup>, Y. LIU<sup>3,2</sup>, Z.-X. WANG<sup>3,2</sup>, M. KABBAJ<sup>1,2</sup>;

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**Abstract:** Social interactions are fundamental for building meaningful relationships and boosting mood. However, social isolation prohibits these interactions and can contribute to a range of negative physical and mental health outcomes. Social isolation is a risk factor for anhedonia, the reduced ability to experience pleasure, which occurs due to a dysregulation in reward processing and reduced motivation. The link between social isolation and anhedonia has been observed in other models, but unlike rats and mice, prairie voles (*Microtus ochrogaster*) exhibit strong peer relationships with one another that is similar to those found in humans. Yet, this link and its underpinnings remain unclear in prairie voles. Here, we assessed whether social isolation in the highly social prairie voles leads to motivational anhedonia. To this end, we used operant conditioning chambers and determined the break point to obtain sugar pellets using a progressive ratio (PR) schedule in both group-housed and socially isolated adult male prairie voles. Using a within-subject design, voles' break points were assessed at baseline, following 2 weeks of isolation/group-housing, and following 4 weeks of isolation/group-housing. After both 2- and 4-weeks of social isolation, isolated subjects showed significantly reduced motivation to obtain access to sucrose pellets when compared to their pre-isolation baseline. Group-housed subjects exhibited similar break points throughout the procedure. These data reveal that, in prairie voles, even a short social isolation (i.e. 2 weeks) leads to signs of motivational anhedonia. We are now performing follow up studies to identify which circuits within the mesocorticolimbic pathway are mediating motivational anhedonia following social isolation.

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**Poster**

**PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H



**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.21/FF6

**Topic:** H.03. Motivation

**Support:** NIH Grant R01 MH125408  
NIH Grant R01 MH108527

**Title:** Oxytocin neurotransmission in the nucleus accumbens mediates avoidance behaviors following social isolation in the socially monogamous female prairie vole

**Authors:** \*F. DUCLOT<sup>1,2</sup>, Y. LIU<sup>3,2</sup>, Z.-X. WANG<sup>3,2</sup>, M. KABBAJ<sup>1,2</sup>;  
<sup>1</sup>Biomed. Sci., <sup>2</sup>Program in Neurosci., <sup>3</sup>Psychology, Florida State Univ., Tallahassee, FL

**Abstract:** Social affiliation is a core characteristic of human social behaviors and its impairments are a common feature related to several neuropsychiatric illnesses including schizophrenia and autism spectrum disorders. In line with the positive health impacts of such affiliative interactions, social isolation is a major risk factor for the development of severe health issues such as anxiety and depression. The socially monogamous prairie vole (*Microtus ochrogaster*) is a highly social rodent displaying peer relationships and interactions akin to those found in humans—including peer bonding—and represents a highly relevant system to study the mechanisms underlying behavioral impairments following social isolation. The oxytocin (OT) neurotransmission in the nucleus accumbens (NAc) is a critical component of prairie voles' social behaviors. Here, we conducted a series of experiments to characterize the role of OT in the NAc in mediating social isolation-induced avoidance behaviors in adult female prairie voles. When compared to co-housed controls, females that experienced 6 weeks of social isolation displayed greater avoidance behaviors in an elevated plus maze test. Isolated females also showed reduced OT receptor (OTR) expression in the NAc as well as a lower number of OT projection neurons from the paraventricular nucleus of the hypothalamus (PVN) to the NAc, when compared to their co-housed counterparts. Notably, avoidance behaviors were increased by the intra-NAc administration of an OTR antagonist in co-housed females, but decreased by the intra-NAc administration of OT in isolated females, thereby suggesting that OT neurotransmission bidirectionally modulates the development of avoidance behaviors following social isolation. To test the underlying circuitry, we targeted the OT projections from the PVN to the NAc using a combination of viral vectors expressing designer receptors exclusively activated by designer drugs (DREADD) with or without OTR antagonism. This chemogenetic inhibition of PVN to NAc projections promoted avoidance behaviors in co-housed females, whereas its activation reduced avoidance behaviors in an OTR-dependent manner in isolated females. Taken together, our data detail the role played by the OT neurotransmission in the NAc in mediating avoidance behaviors following social isolation in adult female prairie voles.

**Disclosures:** F. Duclot: None. Y. Liu: None. Z. Wang: None. M. Kabbaj: None.

**Poster**

**PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.22/FF7

**Topic:** H.03. Motivation

**Support:** NIH/NIDCD 04845 (LMR)  
Schmitt Program for Integrative Neuroscience

**Title:** Activation of ventrolateral prefrontal neurons while observing social interactions

**Authors:** \*L. M. ROMANSKI<sup>1</sup>, M. FUCHS<sup>3</sup>, Y. CAI<sup>1</sup>, M. DILTZ<sup>1</sup>, K. K. SHARMA<sup>2</sup>;  
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**Abstract:** When we watch actors in movies or individuals around us, we interpret actions and develop opinions of the character's personality traits and social status. Brain networks that are activated during social communication and interaction include the ventral frontal lobe. In nonhuman primates, the ventrolateral prefrontal cortex (VLPFC), a proposed homologue of human inferior frontal gyrus, is a locus for the convergence of face and vocal social communication information. Recent studies showed that macaque observers attribute social status roles to conspecifics seen in videos, and that social status can be decoded from amygdala neuronal responses to videos of simulated hierarchical social interactions. In the current study we examined the encoding of social status (dominant, subordinate), identity and vocalization-expression in VLPFC neurons of observer macaques while they viewed audiovisual social interaction videos. The stimuli were created by positioning two separate, conspecific videos side-by-side, depicting two "actor" macaques interacting in a single location, with a dominant making aggressive vocalizations, while the adjacent video showed a subordinate monkey making submissive vocalizations, resulting in a single video of two monkeys "conversing" with one another. We performed neurophysiological recordings using microelectrode arrays (FMAs, Microprobes) implanted in the VLPFC of the observer macaques and tracked eye-movements while they attended audiovisual movies. First, separate videos of 3 conspecific actors making neutral vocalizations and gestures were shown for 4 consecutive days, followed by 4 days of the social interaction videos featuring pairs of the same "actor" monkeys from the neutral videos, then the neutral movies were repeated. Preliminary data includes ~280 single units recorded during 5 sessions of social interaction videos. Our data indicates that observer macaques look at the first vocalization movie (aggressive display) then the second vocalization movie (submissive display) with eye-movements targeting the eyes and the mouths of the "actor" monkeys when vocalizing, with VLPFC neural activity time-locked to the onset of the first video then the second video. We will ascertain if looking time is based on perceived social status and if social status can be extracted from VLPFC single-unit and population data. In addition, we will determine if social status, or perceived identity, is modified by experience, by comparing neural responses to the neutral videos before and after exposure to social interaction videos. Our experiments will provide novel information about the role of VLPFC in social communication.

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**Poster**

## **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.23/FF8

**Topic:** H.03. Motivation

**Support:** K3VR, BMBF Grant 13N16388  
Fraunhofer TALENTA  
NeuroHum, Fraunhofer-Max-Planck Cooperation Grant

**Title:** Personal space in virtual reality assessed with electroencephalography and skin conductance

**Authors:** \***B. NIERULA**, M. LAFCI, A. MELNIK, E. GAUDINOT, S. BOSSE;  
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**Abstract:** Proxemics studies how people perceive and structure surrounding space. Central to proxemics is personal space (PS), the space directly surrounding us and perceived as ours. Personal space boundaries vary within and between individuals (Hayduk, 1981) and are modulated by factors including facial expressions (Ruggiero et al., 2017). PS intrusions trigger arousal and discomfort (Hayduk, 1978), with similar effects reported for human-like virtual intruders (Tootell et al., 2021). Previous research focused on static PS intrusion presentations. We aimed to understand physiological responses to PS violations in a dynamic VR environment, hypothesizing that PS intrusion would increase physiological arousal modulated by facial expressions.

We studied 20 healthy participants (10 females) in immersive virtual reality, which simulates realistic scenarios while maintaining experimental control (Sanchez-Vives & Slater, 2005). Using the passive stop-distance-procedure (Hayduk, 1983), we identified individual comfort distances. In a two-factorial within-subject design, we manipulated distance (PS intrusion vs respect) and avatar facial expression (angry vs neutral), creating 4 conditions with 15 trials each. Each trial began with the avatar at baseline distance for 5 seconds, then approaching toward participants and standing while violating or respecting PS with angry or neutral expressions. We recorded 64-channel EEG, ECG, and GSR signals at 500 Hz using wireless amplifiers (LiveAmp, BrainProducts). Analysis in twelve participants compared electrodermal activity (EDA) among conditions and examined alpha oscillations versus avatar distance using Source Power Comodulation (SPoC) analysis (Dähne et al., 2014).

Linear mixed model analysis identified PS intrusion as the strongest predictor of EDA amplitude: In the standing phase, PS intrusion leads to significantly higher EDA amplitude compared to PS respect ( $\beta = 1.46$ ,  $SE = 0.35$ ,  $t(41) = 5.41$ ,  $p < .01$ ). In the approach phase, EDA amplitude are lower in the than in the stand phase ( $\beta = 0.73$ ,  $SE = 0.36$ ,  $t(41) = -0.23$ ,  $p = 0.05$ ). Preliminary EEG analysis indicates relationships between avatar distance and parietal area activity previously described (Holt et al., 2014; Lloyd et al., 2006; Schienle et al., 2017), likely related to attention mechanisms. Further frequency band analysis with source reconstruction will clarify these observations.

Our findings open avenues for objectively identifying real-time psychophysiological markers of PS intrusion in virtual environments, with implications for developing advanced social interaction applications with virtual characters.

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## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.24/FF9

**Topic:** H.03. Motivation

**Title:** Gender-related differences in electroencephalographic coupling during sexual arousal

**Authors:** \*A. FRÍAS DIMAS<sup>1</sup>, C. AMEZCUA<sup>1</sup>, J. GARCÍA HERNÁNDEZ<sup>1</sup>, R. M. HIDALGO AGUIRRE<sup>2</sup>, M. A. GUEVARA<sup>1</sup>;

<sup>1</sup>Univ. de Guadalajara, Guadalajara, Mexico; <sup>2</sup>Inst. De Neurociencias, Ameca, Mexico

**Abstract:** Sexual arousal (SA) is a complex, multidimensional phenomenon that involves cognitive, emotional, motivational and physiological elements. It has been experimentally elicited in both men and women through the presentation of visual stimuli containing sexual content. Research has identified gender differences in both genital responses and subjective reports of SA following exposure to such stimuli, with men showing a major coincidence between physiological and self-reported measures than women. This disparity may be linked to variations in the EEG coupling (correlation) among the cortical regions involved in processing sexual stimuli, including the prefrontal (PFC), temporal (TC), and parietal (PC) cortices. Several studies have documented a reduced EEG correlation between these cortical areas during SA elicited by sexual stimuli as compared to neutral ones. However, these investigations have generally assessed men and women separately, without directly comparing the gender. Given this context, the present study aimed to explore sex differences in EEG coupling during SA elicited by watching a video with sexual content (VSC). The study included 15 heterosexual men and 15 heterosexual women, whose EEG activity was recorded in the PFC, TC, and PC while viewing a VSC. Although all participants rated the VSC as sexually arousing, the male group (MAG) showed higher EEG correlations between F3-T3 in both slow (theta) and fast (beta1, beta2, gamma) bands, as well as between F4-T4 in slow (delta) and fast (alpha2) bands, compared to the female group (FEG). No significant group differences were found in the correlations between F3-P3 and F4-P4 across any EEG frequency band. The higher intrahemispheric correlation observed in the MAG could be associated to cognitive processing required to exert an inhibitory control on the SA. In contrast, the lower intrahemispheric correlation seen in the FEG suggests that the cortical areas functioned more independently which could reflect a minor inhibitory control, in the laboratory conditions. In summary, the findings show that during SA elicited by

viewing a VSC, men and women shows distinct patterns of EEG coupling, reflecting sex-specific neural processing of sexual stimuli.

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## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.25/Web Only

**Topic:** H.03. Motivation

**Title:** Empathy Patterns: Age, Gender and Cluster Profiles

**Authors:** \*S. ARROYO<sup>1</sup>, F. A. BARRIOS<sup>2</sup>, S. ALCAUTER<sup>3</sup>, D. ATILANO-BARBOSA<sup>4</sup>, V. E. OLALDE<sup>5</sup>, J. ESQUIVIAS<sup>6</sup>;

<sup>1</sup>ENES Juriquilla affiliated to INB UNAM, Querétaro, Mexico; <sup>2</sup>Univ. Nacional Autonoma de Mexico, Querétaro, Mexico; <sup>3</sup>Neurobiología Conductual y Cognitiva, Inst. De Neurobiología. Univ. Nacional A, Queretaro, Mexico; <sup>4</sup>Natl. Autonomous Univ. of Mexico, Queretaro, Mexico; <sup>5</sup>Cognitive and behavioral neurobiology, Inst. De Neurobiología, UNAM, Queretaro, Mexico; <sup>6</sup>Univ. Nacional Autónoma de México, Querétaro, Mexico

**Abstract:** Empathy is essential to our daily lives, enabling deep connections and compassionate responses when we mirror others' joy or suffering. It is a key domain of social cognition for forming and maintaining relationships (Coundouris et al., 2020) and is defined as the ability to infer and share emotional experiences (Schmidt et al., 2017). The Interpersonal Reactivity Index (IRI) measures empathy via four self-report subscales: Perspective Taking (PT) and Fantasy (FS), which assess cognitive empathy (the spontaneous attempt to understand another's viewpoint and the capacity to imagine oneself in fictional situations, respectively); and affective empathy with Empathic Concern (EC) and Personal Distress (PD), EC measures feelings of compassion, concern, and caring in response to others' distress and PD assesses the feelings of anxiety and distress when observing others' negative experiences.

In this study, 393 adults (221 women) aged 18-65 completed the IRI. We examined gender differences, age-related trends, and used data-driven clustering to identify high- and low-empathy groups. Women scored significantly higher than men on EC ( $p=0.0036$ ) and PD ( $p=0.0002$ ). Age correlated negatively with FS ( $r=-0.26$ ,  $p<0.001$ ), EC ( $r=-0.17$ ,  $p=0.0008$ ), and PD ( $r=-0.16$ ,  $p=0.0017$ ), but not PT. K-means clustering yielded two empathy groups designated as high- and low-empathy; using these labels, we trained SVM, LDA, and KNN classifiers, with SVM achieving the highest accuracy (94.07%).

In conclusion, affective components of empathy differ by gender and all subscales decline with age. Clustering revealed distinct high- and low-empathy profiles, and supervised models—particularly SVM—can effectively predict these groups. Empathy underlies our social interactions and linking data-driven empathy clusters to underlying neurobiological and

anatomical structures promises deeper insight into how we attune to others' emotions. This work was supported by SECIHTI scholarships to DAB, VEOM and JMEF and DGAPA-PAPIIT-UNAM grants IN208622 and IN212624.

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## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.26/FF10

**Topic:** H.03. Motivation

**Support:** "Research on conditioning" as part of "Sports in Life" promotion initiative by the Japan Sports Agency  
Toyota Foundation Specific Issues D20-ST-0034

**Title:** Sports Spectating Promotes Social Connection via Interpersonal Heart Rate Synchrony Depending on Playing Experience

**Authors:** \*T. YAMAGUCHI<sup>1,2</sup>, D. FUNABASHI<sup>3</sup>, S. TAKAHASHI<sup>4</sup>, S. DOBASHI<sup>5</sup>, T. MATSUI<sup>6</sup>;

<sup>1</sup>Univ. of Tsukuba, Tsukuba-shi, Ibaraki-ken, Japan; <sup>3</sup>Hlth. and Sport Sci., <sup>2</sup>Univ. of Tsukuba, Tsukuba, Ibaraki, Japan; <sup>4</sup>Doctoral Program in Physical Education, Hlth. and Sport Sciences.,

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**Abstract:** Sports spectating is an inclusive form of engagement accessible across age, gender, and ability, contributing to reduced loneliness and enhanced well-being. These benefits may be supported by oxytocin-driven social brain mechanisms including interpersonal physiological synchrony, as seen in social interactions such as eye contact with pets. Indeed, in-person sports spectating enhances heart rate synchrony (HRS) among spectators; however, oxytocin dynamics and effective strategies to enhance HRS during spectating remain unclear. Given that narrative comprehension facilitates interpersonal synchrony and social bonding, we thus hypothesized that sports spectating enhances oxytocin production and promotes interpersonal HRS and social bonding depending on prior playing experience. We first examined whether sports spectating promotes HRS among individuals with playing experience. 10 basketball players (10 males,  $18.7 \pm 0.8$  years) were recruited to watch a university basketball game. Heart rates were continuously recorded during spectating, and HRS was calculated up to halftime (HT). At the end of HT, participants completed questionnaires assessing their sense of unity with the players and spectators. The results showed that HRS among players increased and positively associated with their sense of unity. Next, we assessed the influence of playing experience. We recruited 44 general spectators (26 males,  $23.8 \pm 9.5$  years) and 18 basketball players (14 males,  $18.8 \pm 0.8$  years). Heart rates were continuously recorded separately for during play and outside of play.

Saliva samples and psychological questionnaires (unity, psychological flow, loyalty) were collected at pre-game, post-game, and 15 minutes later. Salivary oxytocin and cortisol were assessed, and oxytocin/cortisol (OC) ratio was calculated. Salivary oxytocin levels did not increase, but cortisol levels decreased in both groups. As a result, OC ratio increased, indicating a neuroendocrine state more conducive to social bonding. Average, peak heart rates and HRS increased in both groups during and outside of play, with a more pronounced effect among players. Mediation analysis revealed that HRS during play enhanced flow via unity with players, while HRS outside of play promoted loyalty via unity with spectators. Our findings suggest that sports spectating enhances oxytocin-mediated hormonal balance and promotes social connection via HRS depending on playing experience. Playing experience in sports enhance flow state and socio-physiological responses during spectating, fostering an active lifestyle for well-being through reduced loneliness.

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## **Poster**

### **PSTR236: Social Communication and Behavior Across Species**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR236.27/FF11

**Topic:** H.03. Motivation

**Title:** Pre-match carbonated water consumption enhances physiological synchrony and team bonding in esports competition: a crossover study

**Authors:** \*R. KASAHARA<sup>1</sup>, S. TAKAHASHI<sup>2</sup>, S. DOBASHI<sup>3</sup>, W. KOSUGI<sup>5</sup>, S. MIZUNO<sup>6</sup>, T. MATSUI<sup>4</sup>, T. YUKINA<sup>3</sup>;

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**Abstract:** Teamwork during esports play is predicted by intra-team heart rate synchrony (HRS), yet effective strategies to enhance HRS and teamwork remain unclear. Shared sensory or motor experiences can foster group cohesion and cooperative behavior. Carbonated water consumption reduces cognitive fatigue and promotes a sense of fairness and enjoyment in solo esports play. We thus hypothesized that shared consuming carbonated water enhances physiological synchrony and facilitate social bonding and teamwork in esports competition. To test this hypothesis, we first examined whether carbonated water promotes intra-team HRS and teamwork during esports play. Twenty young adult males ( $22.4 \pm 2.1$  years) formed four teams (five players each) and competed in the team-based esports *Valorant*. In a randomized crossover design, each team consumed either 200 mL of carbonated water (CW) or fresh water (FW) immediately before the match. Although individual performance metrics (e.g., headshots, body

shots, leg shots percentages) did not differ by condition, the number of assists—a proxy for teamwork—was approximately twice as high in the CW condition. Total team eliminations were also higher in the CW condition. Mean heart rate rose to approximately 110 bpm during matches, with no significant difference between conditions. However, intra-team HRS increased during esports play in both conditions and was significantly higher in the CW condition. Notably, in the CW condition, intra-team HRS positively correlated with the number of assists. Self-reported team cohesion and team flow were also significantly higher post-match in the CW condition. We next assessed the effect of synchronized consumption of carbonated water by both competing teams. Using the same protocol, both teams in each match consumed the same beverage (either CW or FW), ingesting 200 mL immediately before the match. As in the previous experiment, mean heart rate did not differ between conditions. However, inter-team HRS following the match was significantly higher in the CW condition. In addition, pupil diameter—an indirect marker of noradrenergic and dopaminergic activity—was significantly greater in CW condition during play. The CW condition also elicited a deeper flow state during play and stronger perceived unity with opponents post-match. Our findings provide the first evidence that carbonated water consumption enhances both intra- and inter-team physiological synchrony, thereby promoting social bonding and teamwork in esports competitions. Carbonated water could be a novel, health-compatible strategy to enrich social dynamics in competitive digital environments.

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## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.01/FF12

**Topic:** H.03. Motivation

**Support:** CSIC-Udelar Grant

**Title:** Pup-directed aggression toward newborns in mice: An impulsive-like behavior?

**Authors:** \***D. E. OLAZABAL**, M. ALSINA-LLANES;  
Facultad De Medicina, Udelar, Montevideo, Uruguay

**Abstract:** Infanticidal or pup-directed aggressive behavior is present in most species, including humans. It occurs in both reproductive and non-reproductive contexts and its incidence and biological basis may vary among species, strains, sex, and individual experiences. We describe the most likely neural circuit that mediates aggressive behavior towards pups in mice and show



that repeated non-contact exposure to pups (to prevent immediate attack), with or without movement restriction and social isolation, can inhibit infanticidal behavior and increases the incidence of parental behavior in male mice (CB57Bl6). Besides, the frequency of pup-directed aggression was not associated with the levels of male-male aggression in a resident-intruder test. This study shows that the experience of being exposed to newborns without contact with them can inhibit the highly driven impulsive-like attacking behavior towards pups and facilitate parental behavior. Our results suggest that aggressive behavior towards pups can be blocked in naïve male mice, and that this behavior differs from male-male aggression. We propose a neural model to explain aggressive behavior towards pups and discuss evidence suggesting that infanticidal and pup-directed aggressive behavior, although hard-wired in the brain, can be blocked or inhibited by changing the experiences of the subject prior to the access to pups.

**Disclosures:** D.E. Olazabal: None. M. Alsina-Llanes: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.02/GG1

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** NIH Grant DA055202  
Western University of Health Sciences

**Title:** D2 receptor regulation of pain-induced impulsive choice in rats

**Authors:** \*A. NAZARIAN<sup>1</sup>, A. TSENG<sup>2</sup>, E. FELIX<sup>3</sup>;

<sup>1</sup>Western Univ. Hlth. Sci., Pomona, CA; <sup>2</sup>Western Univ. of Hlth. Sci., Moreno Valley, CA;

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**Abstract:** Impulsivity is characterized by a deficit in planning and making choices for immediate gratification with reduced concern for long-term negative outcomes. While impulsivity is a personality trait encompassing a normal spectrum among healthy individuals, an excess of impulsive choices is associated with a wide range of maladaptive behaviors and adverse life events. Patients with chronic pain show higher impulsivity, and this is associated with the development of psychiatric comorbidities including anxiety and depression as well as a higher risk for the misuse of drugs of abuse. It is therefore important to understand the mechanisms underlying pain-induced impulsivity to better treat chronic pain and its associated manifestations. Previously, we showed that persistent inflammatory pain manipulation increased impulsive choice in rats using a delay discounting task (DDT). The pain-induced impulsive choice was blocked by morphine and amphetamine, suggesting a distinct role of dopamine in processing pain-induced impulsivity. Given the regulatory actions of D2 receptors on general impulsivity, we sought to examine the role of dopamine D2 receptors on pain-induced impulsive choice using the DDT. Male and female Sprague-Dawley rats were trained in the DDT and

persistent inflammatory pain was induced by hind paw injection of complete Freund's adjuvant (CFA). Impulsivity was measured in which rats were given a choice between a lever providing a small amount of food delivered immediately or one providing a larger amount of food delivered after a delay. Rats were categorized as either high- or low-impulsive according to their baseline response. CFA treatment gradually heightened impulsivity in high- and low-impulsive rats. To test the effect of D2 receptors, rats were pretreated with raclopride (D2 receptor antagonist), or saline before daily testing sessions. Preliminary findings suggest that raclopride reduced pain-induced impulsivity in high- and low-impulsive males, whereas the effects of the drug in females were more modest. These preliminary results suggest a regulatory effect of D2 receptors on pain-induced impulsivity.

**Disclosures:** A. Nazarian: None. A. Tseng: None. E. Felix: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.03/GG2

**Topic:** H.06. Anxiety Disorders

**Support:** Hartwell Postdoctoral Fellowship  
NIH Grant R21EY02945  
NIH Grant R01MH12015  
NIH Grant R01MH12543  
NIH Grant 1DP1MH13270  
Hope for Depression Research Grant  
Duke University School of Medicine MedX Grant

**Title:** Prevention of excessive grooming in OCD model through engineered gap junction circuit editing

**Authors:** \*K. K. WALDER-CHRISTENSEN<sup>1</sup>, K. DZIRASA<sup>2</sup>;

<sup>1</sup>Duke Univ., Durham, NC; <sup>2</sup>Duke Univ. Med. Ctr., Durham, NC

**Abstract:** OCD is a debilitating neuropsychiatric condition effecting ~2% of the population worldwide. OCD is diagnosed by the presence of intrusive thoughts and compulsive repetitive behaviors performed in response to the intrusive thought. Treatments for OCD include psychotherapy and serotonin reuptake inhibitor medications but are not effective in a third of patients. Neuroimaging has revealed altered activity in corticostriatal circuits in people with OCD. Sapap3<sup>-/-</sup> mice are used as a model for OCD due to behavioral observation of self-lesioning, effective treatment with the serotonin reuptake inhibitor, fluoxetine. Since this model was established several decades ago, the circuit underlying this behavior has been well characterized and attributed to abnormal corticostriatal activity specifically in the OFC to striatum circuit. Our lab has developed a gap-junction based tool for manipulating circuits-

LinCx (long term integration of circuits using connexins) that we deploy here in a cell-type specific dependent manner to alter the synchrony between OFC and major neuron classes in the striatum. LinCx editing in juvenile Sapap3<sup>-/-</sup> mice in OFC to PV<sup>+</sup> Striatal neurons decreases the development of pathological grooming with no effect on anxiety behavior. However, LinCx targeting in these mice between OFC and D2 striatal neurons increases anxiety behaviors, indicating that compulsive behaviors and anxiety are orthogonally encoded behaviors in the striatum. Finally, we utilize high density recordings in striatum along with LFP recordings in OFC to show that LinCx alters the synchrony of striatal cell firing to OFC oscillations indicating spike-timing as a targetable mechanism for disease pathology. Thus, we demonstrate the utility of a novel gap junction synchrony tool in a genetically defined model of neuropsychiatric synapse dysfunction.

**Disclosures:** K.K. Walder-Christensen: None. K. Dzirasa: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.04/GG3

**Topic:** H.03. Motivation

**Support:** NIH Grant U01DA055017

**Title:** Linking compulsive behavior across obesity, eating disorders and drug addiction via punishment-reactive ‘brake’ neurons in the rostromedial tegmental nucleus (RMTg).

**Authors:** \*R. N. A. OWUSU MENSAH<sup>1</sup>, T. KERR<sup>1</sup>, C. WAKAYAMA<sup>1</sup>, A. SMITH<sup>1</sup>, S. VETTLESON-TRUTZA<sup>2</sup>, A. O'BRIEN<sup>1</sup>, S. GRIJALVA<sup>3</sup>, H. NEDELESCU<sup>4</sup>, N. J. O'CONNOR<sup>5</sup>, J. GLASER<sup>5</sup>, B. T. HOPE<sup>6</sup>, T. C. JHOU<sup>7</sup>, N. SUTO<sup>1</sup>;

<sup>1</sup>Mol. Pharmacol. and Exptl. Therapeut., <sup>2</sup>Mayo Clin., Rochester, MN; <sup>3</sup>The Univ. of Texas at El Paso, El Paso, TX; <sup>4</sup>Neurosci., Scripps Res. Inst., San Diego, CA; <sup>5</sup>MBF Biosci., Williston, VT; <sup>6</sup>Behav Neurosci, NIH/NIDA, Baltimore, MD; <sup>7</sup>Neurosci., Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD

**Abstract:** Along with obesity, binge eating disorder (BED) and bulimia nervosa (BN) - as examples of “food addiction” - share similar behavior and brain profiles with substance use disorders (SUD) suggesting a common cause. Like drug craving and use in patients with SUD, food craving and eating in patients with BED/BN as well as some obese individuals can persist despite adverse consequences (punishments). We previously reported, as with extensive exposure to obesogenic diet high in fat and sugar, extensive exposure to cocaine or alcohol - known to cause addiction-like brain changes and punishment-resistant “compulsive” drug intake in rats - can cause similarly punishment-resistant “compulsive” food intake in rats (Laque et al., 2022, *British Journal of Pharmacology*, 179:2589-2609). Food intake is thought to be regulated by both “homeostatic” (metabolic/caloric) and “non-homeostatic” (hedonic/incentive) systems in

the brain. Our findings suggest that compulsive food intake following extensive exposure to cocaine, alcohol or obesogenic diet is driven by non-homeostatic - rather than homeostatic - dysregulation (e.g., craving snacks even when not hungry). Thus, similarly common - rather than drug or diet-specific - changes in the brain “reward circuits” known to regulate drug and food intake independently of caloric needs likely underlie compulsive behavior across obesity, eating disorders and drug addiction. Punishment suppresses appetitive behavior in part by recruiting neurons in the rostromedial tegmental nucleus (RMTg). Here, we will report that extensive exposure to cocaine, alcohol or obesogenic diet all results in diminished neural punishment-reactivity in RMTg, thereby potentially identifying punishment-reactive ‘brake’ neurons in this brain site as a common cellular target to link compulsive behavior across obesity, eating disorder and drug addiction.

**Disclosures:** R.N.A. Owusu Mensah: None. T. Kerr: None. C. Wakayama: None. A. Smith: None. S. Vettleson-Trutza: None. A. O'Brien: None. S. Grijalva: None. H. Nedelescu: None. N.J. O'Connor: None. J. Glaser: None. B.T. Hope: None. T.C. Jhou: None. N. Suto: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.05/GG4

**Topic:** H.06. Anxiety Disorders

**Support:** First-Year Research Immersion Program, Binghamton University

**Title:** Novel rat model of a sudden reduction of high social enrichment demonstrates behavioral validity for obsessive-compulsive disorder (repetitive arm choice and excessive grooming)

**Authors:** \*G. J. BAGATELL<sup>1</sup>, T. A. BOHNKE<sup>1</sup>, D. S. KREISS<sup>1,2</sup>;

<sup>1</sup>Binghamton Univ., Binghamton, NY; <sup>2</sup>Binghamton University, First-Year Res. Immersion Program, Neurosci. Stream, Binghamton, NY

**Abstract:** Obsessive-compulsive disorder (OCD) is a chronic mental health condition characterized by anxiety, persistent/intrusive thoughts, and repetitive behaviors performed in an attempt to mitigate distress. OCD symptom severity and frequency were exacerbated by the limited social interactions imposed by the COVID-19 lockdowns. This study evaluated a novel rat model simulating the effects of a sudden reduction of social enrichment on OCD-like behaviors. Male (n=28) and female rats (n=28) were exposed to 5.5 weeks (Day 33-73) of high social enrichment. This included housing in larger cages with enrichment toys, frequent 5-minute individual handling sessions, and 20-minute ‘playdates’ with 13 other rats of the same sex (4 sessions per week, in a large open field with multiple toys). For the 5.5 weeks following (Day 74-112), Experimental rats were deprived of these social interactions and housed in standard cages, while Control rats continued to experience high social enrichment. The effects of the

reduction of high social enrichment on OCD-like behaviors were assessed through grooming in an open arena and arm choice in an Elevated T-Maze (2 closed arms and 1 exposed arm). Results demonstrated that the reduction of social enrichment led to increased OCD-like behaviors in males and females. Females experiencing the reduction of social enrichment exhibited an increased number of grooms. Males experiencing the reduction of social enrichment displayed persistence of grooming, as they did NOT exhibit the decrease in number of grooms and total time spent grooming that the male rats experiencing continued high enrichment did. In the Elevated T-Maze, females experiencing the reduction of social enrichment exhibited an increased number of same arm choices. Males experiencing the sudden reduction of social enrichment showed persistence of choosing the same arm and making a closed arm choice, as they did NOT exhibit the decrease in same arm choices and the increased 'no choices' (remaining in the exposed arm) that the male rats experiencing continued high enrichment did. These findings show that after the removal of enrichment, males increased not only in repetitiveness, but also in anxiety. These findings suggest that a sudden reduction of social enrichment exacerbates the expression of OCD-like behaviors, thereby supporting the face validity of this novel model. This experimental paradigm could serve as a valuable tool for further investigation of the mechanisms underlying OCD and the role of social interaction, as well as the potential development of more effective therapeutic strategies for this debilitating disorder.

**Disclosures:** G.J. Bagatell: None. T.A. Bohnke: None. D.S. Kreiss: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.06/GG5

**Topic:** H.06. Anxiety Disorders

**Support:** First-Year Research Immersion Program, Binghamton University  
Binghamton Undergraduate Research Award

**Title:** Novel approach for analyzing neurochemical data: Box-Cox transformation and generalized linear model with adherence to conservative statistical criteria

**Authors:** \*A. HEPNER<sup>1</sup>, D. S. KREISS<sup>2</sup>;

<sup>2</sup>First-Year Res. Immersion Program, Neurosci. Stream, <sup>1</sup>Binghamton Univ., Binghamton, NY

**Abstract:** Published data concerning measurement of neurochemical levels are typically analyzed using analysis of variance (ANOVA). However, most analyses are performed without explicitly verifying proper statistical assumptions of linearity, independence, normality, and homoscedasticity. Application of ANOVAs to data that violates the required assumptions conflicts with existing statistical protocols and may lead to misinterpretation of results. The aim of this study was to employ conservative statistical criteria to determine the effects of sudden

removal of high social enrichment on monoaminergic neurochemical levels in rats. In the novel experimental paradigm, both male (n=28) and female (n=28) rats were exposed to 5.5 weeks of high social enrichment (larger cages, frequent 5-minute handling, 20-minute 'playdates' with 13 other rats 4 times/week). For the 5.5 weeks following, experimental rats were deprived of these social interactions, while the control rats continued to experience high social enrichment. To determine the neurophysiological effects of removal of high social enrichment, neurochemical levels in post-mortem tissue were measured using High Performance Liquid Chromatography paired with electrochemical detection. Neurochemical levels of the dopamine metabolite DOPAC in the lateral thalamus were chosen as an exemplary data set for the current investigative study. Analysis of the data using a "typical" approach for statistical evaluation was compared to analysis using a novel approach. For the typical approach, outliers more than 2 standard deviations from the mean were removed. Then, without consideration of statistical assumptions, a two-way ANOVA was used to determine the effects of Sex and Enrichment. For the novel approach, adherence to necessary statistical assumptions was first evaluated. Upon uncovering violations in normality and heteroscedasticity, the Box-Cox method of power transformations was then deployed to transform the data to better fit to a linear model. Analysis using the typical approach showed that experimental treatment significantly increased DOPAC in the lateral thalamus [ $F(1,48) = 5.30$ ,  $p = 0.026$ ]. However, that effect disappeared when the data analyzed using the novel approach ( $p > 0.05$ ,  $r^2 = 0.058$ ). Analysis of this exemplary data set demonstrates the potential for misinterpretation that can result from failing to evaluate proper statistical assumptions. Application of generalized linear models enhances the ability to correctly interpret neurochemical findings and to derive appropriate conclusions.

**Disclosures:** A. Hepner: None. D.S. Kreiss: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.07/GG6

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** CLA Faculty Small Grant

**Title:** Fentanyl-induced sensitization and cross-sensitization to morphine in adolescent male and female rats

**Authors:** \*E. N. SIU, A. R. ZAVALA, T. G. MORRIS;  
Psychology, California State Univ., Long Beach, CA

**Abstract:** Fentanyl is a potent synthetic mu-opioid receptor agonist that has driven a surge in overdose deaths in the last 10 years. Adolescents are especially vulnerable to the effects of fentanyl exposure, as drug use often starts during this developmental period. Notably, the percentage of individuals aged 13-19 exposed to fentanyl who reported intentional use of

fentanyl increased from 31.4% to 51.4% in 2021. Surprisingly, the neurobiological and behavioral effects of fentanyl in adolescents remain understudied. Behavioral sensitization is an animal model of neuroplasticity that reflects changes in brain circuitry and manifests as an enhancement of the behavioral effects of repeated drug administration. For example, adult animals exhibit increased locomotion and rearing after repeated fentanyl administration. Importantly, few studies have investigated fentanyl-induced sensitization in adolescent rats. The present study examined the effects of fentanyl administration in late adolescent male and female rats. Specifically, rats were given saline or fentanyl (5, 15, 45, or 135 µg/kg) during postnatal days (PD) 40-49, and their horizontal distance traveled was assessed for 120 min. Rats were then challenged with saline or 45 µg/kg of fentanyl on PD 51, and sensitized responses were evaluated for 150 min. To examine cross-sensitization with morphine, rats were challenged with saline or 20 mg/kg of morphine on PD 52. Preliminary results indicate that adolescent rats exhibit fentanyl sensitization in a dose-dependent manner during the pretreatment phase, and a dose-dependent heightened locomotor response to the fentanyl and morphine challenges. Findings from the present study contribute to the growing body of literature regarding opioid responses in adolescent rats. Future studies will investigate whether the effects observed in the present study are unique to the adolescent period.

**Disclosures:** E.N. Siu: None. A.R. Zavala: None. T.G. Morris: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.08/GG7

**Topic:** G.03. Stress and the Brain

**Support:** NIH Grant R01DA053328

**Title:** The role of prelimbic dopamine receptors 1 and 2 in cue-induced sucrose seeking

**Authors:** \*D. GONZALEZ<sup>1</sup>, L. GAEDE<sup>1</sup>, A. LOPEZ<sup>1</sup>, R. LILJEDAHN<sup>1</sup>, F. CANO<sup>3</sup>, A. G. LEE<sup>2</sup>, E. MI<sup>1</sup>, L. TIMONI<sup>1</sup>, K. K. SZUMLINSKI<sup>4</sup>;

<sup>1</sup>UC Santa Barbara, Santa Barbara, CA; <sup>2</sup>UC Santa Barbara, San Diego, CA; <sup>3</sup>Psychological and Brain Sci., Univ. of California Santa Barbara, Santa Barbara, CA; <sup>4</sup>Psychological and Brain Sci., Univ. California-Santa Barbara, Santa Barbara, CA

**Abstract:** The dramatic rise in the consumption of highly palatable foods, including those high in sugars such as sucrose, has contributed to a global obesity epidemic that is currently being faced today. Neutral stimuli in the environment can, after repeated pairings with a palatable food, become a food cue that elicits seeking of the food. Dopamine, a neurotransmitter important in reward and motivation, and plays a role in cue-induced seeking behavior. The medial prefrontal cortex is critical for sugar's reinforcing properties that motivate food seeking and eating, but the involvement of the prelimbic aspect of the medial prefrontal cortex has not been extensively

studied, nor is the functional relevance of dopamine receptors within the prelimbic cortex known. The current study attempted to address this gap in knowledge. Male and female Sprague-Dawley rats were trained in an operant chamber using a self-administration paradigm to press a lever to receive a sucrose pellet alongside a light and tone compound stimulus that served as a sucrose cue. Following acquisition of sucrose seeking behavior, animals underwent a cue test wherein pressing on the active lever resulted in the presentation of the sucrose cue alone but no delivery of a sucrose pellet. Immediately before being placed in the operant chamber to start the cue test, rats received a microinjection of a dopamine receptor 1 antagonist, dopamine receptor 2 agonist, dopamine receptor 2 antagonist, or vehicle in the prelimbic cortex, and the amount of active lever pressing during the cue test was recorded and compared to determine the effect of treatment on cue-induced sucrose seeking. Only the dopamine receptor 2 agonist quinpirole reduced cue-induced sucrose seeking, implicating dopamine receptor 2 activation within the prelimbic cortex in cue-induced motivated food seeking behaviors.

**Disclosures:** D. Gonzalez: None. L. Gaede: None. A. Lopez: None. R. Liljedahl: None. F. Cano: None. A.G. Lee: None. E. Mi: None. L. Timoni: None. K.K. Szumlinski: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.09/GG8

**Topic:** H.06. Anxiety Disorders

**Support:** First-Year Research Immersion Program, Binghamton University

**Title:** Novel rat animal model of a sudden reduction of high social enrichment demonstrates behavioral and in vitro monoaminergic neurochemical validity for addiction

**Authors:** \*Y. WATANABE<sup>1</sup>, P. G. GOODEVE<sup>1</sup>, D. S. KREISS<sup>2</sup>;

<sup>1</sup>Binghamton Univ., Binghamton, NY; <sup>2</sup>Binghamton University, First-Year Res. Immersion Program, Neurosci. Stream, Binghamton, NY

**Abstract:** Addiction, a behavioral condition characterized by repetition, reinforcement, and neurophysiological alterations, markedly increased during and following social restrictions associated with the COVID-19 pandemic. This study assessed the validity of a novel animal model that was designed to simulate the effect of the removal of high social enrichment on addictive-like behaviors and neurochemistry. Male (n=28) and female (n=28) Sprague-Dawley rats were habituated to high social enrichment for 5.5 weeks (Day 33-73). High social enrichment consisted of 20-minute ‘playdates’ with 13 other rats 4 times a week, frequent researcher handling, and pair-housing in larger cages with multiple toys. For the following 5.5 weeks (Day 74-112), the Control rats continued high social enrichment, whereas the Experimental rats were exposed to standard social enrichment with no playdates, minimal handling, and standard pair-housing conditions. Spontaneous arm choice in an Elevated T-Maze



and grooming in an open field were assessed as addictive-like behaviors. The ventral striatum and prefrontal cortex were targeted for post-mortem neurochemical analysis as they mediate reward and behavioral routine. High-performance liquid chromatography (HPLC) paired with electrochemical detection was used to measure levels of dopamine (DA), serotonin (5-HT), norepinephrine, 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxyindole-3-acetic acid (5-HIAA), dopamine turnover (DOPAC/DA), and serotonin turnover (5-HIAA/5-HT). Reduced social enrichment increased repetitive arm choices and grooming in both sexes, showing strong behavioral validity for the model's reflection of the increased rates of addiction seen following the social isolation of the pandemic. In addition to noradrenergic changes in the prefrontal cortex, dopaminergic changes in both the prefrontal cortex and ventral striatum provided complementary neurochemical validity as they reflect neurophysiological alterations in human addicts. Reduced social enrichment eliminated, as well as induced, behavioral and neurochemical sex differences - evidence of differential effects of reduced enrichment across subsets of a species. This model shows potential promise for translational research into the interaction of social enrichment and addiction.

**Disclosures:** Y. Watanabe: None. P.G. Goodeve: None. D.S. Kreiss: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.10/GG9

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** FWF P35053

**Title:** Role of Satb2 in cocaine memory and relapse

**Authors:** \*D. G. MONTEIRO, M. OBWALLER, I. M. AMARAL, A. HOFER, R. EL RAWAS;

Dept. of Psychiatry, Psychotherapy, Psychosomatics and Med. Psychology, Univ. Clin. for Psychiatry I, Med. Univ. Innsbruck, Innsbruck, Austria

**Abstract:** Drug addiction arises as a significant public health challenge, impacting individuals and societies at large. While substantial progress has been made in understanding the neurobiological underpinnings of addiction, certain aspects remain unresolved. Satb2 is a DNA-binding protein involved in gene expression regulation through chromatin remodeling. The Satb2 conditional mutant mouse (cKo) (Satb2 flox/flox::Camk2a-Cre), which lacks Satb2 expression in the cortex and CA1 region of the hippocampus from the third postnatal week, shows deficits in long-term memory. This study aims to characterise the model with a specific focus on appetitive memory related to addiction, investigating behavioural and molecular alterations linked to drug-associated learning. Using the Conditional Place Preference (CPP) paradigm, we compared reinstatement to cocaine induced by cocaine priming, as well as by stress (Forced swim test -

FST), between Satb2 cKO and floxed control mice. These mice did not differ in the extinction rate or the reinstatement to cocaine; nevertheless, we observed a significant increase in immobility time in the FST between the two groups of mice. These results suggest that Satb2 in the cortex and hippocampus is not involved in reinstatement to cocaine CPP and that Satb2 cKo mice show increased despair-like behaviour. We then examined regional Satb2 expression in cKo compared to controls. Among the brain regions analyzed, the paraventricular nucleus of the thalamus (PVT) retains Satb2 expression in both conditional Satb2 cko and control mice. Given prior evidence of Satb2 upregulation in the PVT following cocaine conditioning, we are selectively knocking down Satb2 in this region to investigate its functional role in cocaine-seeking behaviour and relapse. We are also investigating brain regions in which Satb2-expressing neurons are activated in association with the persistence of drug-related memories. These efforts are expected to yield critical insights into the molecular mechanisms underlying cocaine addiction and may inform the development of more effective pharmacological strategies to prevent relapse. This Research is in collaboration with the Institute for Neuroscience (MUI)

**Disclosures:** D.G. Monteiro: None. M. Obwallner: None. I.M. Amaral: None. A. Hofer: None. R. El Rawas: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.11/GG10

**Topic:** H.04. Emotion

**Title:** Rats high in acute withdrawal from amphetamine and morphine have a lower bout amplitude than those low in withdrawal

**Authors:** \*W. WHITE, I. M. WHITE;  
Morehead State Univ., Morehead, KY

**Abstract:** Previously, when rats were given a psychostimulant (2.0 mg/kg amphetamine) or an opioid (5.0 mg/kg morphine), 13-24 hours later they were around 25% less active, on average, than following saline. The reduction in activity was a sign of acute withdrawal. Different individuals showed lower (low withdrawal) or higher (high withdrawal) reductions in activity following amphetamine and morphine. This research assessed how amphetamine and morphine affected bout organization in these different individuals. Normally, rats are active in bouts or episodes that are around 20 minutes in duration and that occur approximately every two hours. Adult male Wistar rats were treated with saline, amphetamine (N=24), or morphine (N=25), and their activity (distance moved) was monitored in open fields for 24 hours. Treatments occurred near light onset of a 12/12 hour light/dark cycle. The number of bouts, the time between bouts, the duration of bouts, and the amplitude of bouts were compared for low and high withdrawal individuals. For both amphetamine and morphine, the difference between low and high withdrawal animals involved bout amplitude: High withdrawal animals had a lower bout

amplitude. Other bout parameters did not differ. The difference between low and high acute withdrawal entailed the same change in bout organization for amphetamine and morphine, suggesting these drugs produce acute withdrawal through a common mechanism. In addition, the basic organization of episodes was intact even in high withdrawal animals, providing evidence that different mechanisms are involved in acute withdrawal and in the basic organization of episodic activity.

**Disclosures:** W. White: None. I.M. White: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.12/GG11

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** Faculty Small Grant from the College of Liberal Arts

**Title:** Cp 809101, a selective serotonin (5-HT)<sub>2C</sub> receptor agonist, attenuates the expression of methamphetamine preference in adolescent male and female rats.

**Authors:** \*M. ROACH<sup>1</sup>, A. LIN<sup>1</sup>, T. TRAN<sup>1</sup>, N. PENTKOWSKI<sup>2</sup>, A. R. ZAVALA<sup>1</sup>;  
<sup>1</sup>Psychology, California State Univ., Long Beach, CA; <sup>2</sup>Univ. of New Mexico, Albuquerque, NM

**Abstract:** Methamphetamine (METH) use during adolescence is detrimental, as it leads to poor treatment outcomes later in life. Additionally, there are currently no FDA-approved medications for the treatment of METH use disorder. Studies have shown that activation of the serotonin (5-HT) 2C receptor is associated with a decrease in the rewarding effects of psychostimulants like cocaine and methamphetamine. Indeed, lorcaserin, a 5-HT<sub>2C</sub> receptor agonist, underwent clinical trials for the treatment of cocaine use disorder but failed and was later removed from the market by the FDA due to side effects. Despite this, the 5-HT<sub>2C</sub> receptor may still hold promise as a potential pharmacological therapeutic for substance use disorder, particularly if more selective and potent agonists are employed. Thus, this project investigated whether CP 809101, a more selective 5-HT<sub>2C</sub> receptor agonist, was effective at reducing the expression of METH-induced conditioned place preference (CPP) in male and female adolescent rats. On day 1, habituation, rats were confined to each side of a two-chamber CPP apparatus for 10 mins. On days 2-4, baseline, rats had free access to both sides of the apparatus for 30 min. During days 5-12, conditioning, rats were injected on alternating days with METH (0.0, 0.125, or 0.5 mg/kg, intraperitoneally) or saline and were immediately confined to one side of the apparatus for 30 min. During day 13, testing 1, rats were pretreated with CP 809101 (0.0 or 0.15 mg/kg, subcutaneously) 30 min before having free access to both sides of the apparatus for 30 min. On day 14, rats were left alone in their cages. A second test day occurred on day 15, during which rats had free access to both sides of the apparatus for 30 min in a drug-free state. Preliminary

results indicate that rats exhibit METH preference to the 0.5 mg dose of METH, and that the preference is attenuated with pretreatment with CP 80901. These results suggest that targeting the 5-HT<sub>2C</sub> receptor system with a more selective agonist is effective in reducing METH-seeking behavior in adolescent male and female rats, and adds to the preclinical data examining this receptor system in adult animals.

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## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.13/GG12

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Title:** Transgenerational effects of paternal alcohol consumption on offspring brain and behavioral development

**Authors:** \*K. E. CONNER<sup>1,2</sup>, R. F. PEREZ, Jr.<sup>4,3</sup>, K. J. HUFFMAN<sup>3,2</sup>;

<sup>1</sup>Psychology, California State University, Dominguez Hills, Carson, CA; <sup>2</sup>Neurosci.,

<sup>3</sup>Psychology, Univ. of California, Riverside, Riverside, CA; <sup>4</sup>Psychology, Norco Col., Norco, CA

**Abstract:** Fetal alcohol spectrum disorders (FASD) describe the wide array of long-lasting developmental abnormalities in offspring caused by prenatal alcohol (ethanol [EtOH]) exposure via maternal gestational drinking. Although the teratogenic consequences of prenatal EtOH exposure are apparent, the effects of preconception paternal EtOH exposure (PatEE) are still unclear. In previous rodent models, PatEE has been shown to disturb gene expression in the brain (Finergersh & Homanics, 2014; Rompala et al., 2017) and liver (Chang et al., 2017, 2019) of offspring. Our previous research suggests that PatEE can induce molecular changes and abnormal behavior in the offspring in the first filial generation (F1) (Conner et al., 2020). However, it is not known whether the effects of PatEE can be passed transgenerationally. In this study, we utilized a novel mouse model of PatEE where male mice self-administered 25% EtOH for 15-20 days prior to conception, generating indirect exposure to the offspring (F1) through the paternal germline. PatEE (F1) males were paired with EtOH naïve females to generate offspring for the second generation (F2). The impact of paternal ethanol exposure on offspring neocortical development was evaluated using neuroanatomical and molecular techniques at postnatal day (P) 0, as well as a battery of behavioral assays in pre- and peri-pubescent mice (P20 and P30). We observed no differences between control and PatEE (F1 and F2) mice in measures of neocortical length. Crucial cortical patterning genes, *Id2* and *RZRβ*, displayed abnormal patterning in the F1 generation with recovery at F2 at P0. Additionally, PatEE may generate sex-specific effects on offspring behavior as shown by the suok test, forced swim test, accelerated rotarod, and elevated plus maze. These effects can last up to two generations after the sire's initial exposure. However,

no significant changes in sociability were observed in the 3-chambered sociability test. Overall, these findings suggest that ethanol exposure in males prior to conception may induce long-lasting, transgenerational changes in the brain and behavior of offspring. This study provides additional insight into the biological mechanisms that potentially underlie atypical behavior observed in children of alcoholic fathers.

**Disclosures:** K.E. Conner: None. R.F. Perez: None. K.J. Huffman: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.14/GG13

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** University of Michigan Research Scouts Program OORRS033123

**Title:** Chronic semaglutide (Ozempic®) enhances the incentive motivational value of a food reward and associated cue

**Authors:** \*D. PEREIRA<sup>1</sup>, S. E. CHANG<sup>1</sup>, N. N. MORALES<sup>4</sup>, C. A. TURNER<sup>2</sup>, S. B. FLAGEL<sup>3</sup>;

<sup>2</sup>Psychology, <sup>3</sup>Michigan Neurosci. Inst., <sup>1</sup>Univ. of Michigan, Ann Arbor, MI; <sup>4</sup>Univ. of Puerto Rico, Trujillo Alto, Puerto Rico

**Abstract:** Obesity is a major public health concern in the United States. Glucagon-like peptide 1 (GLP-1) receptor agonists like semaglutide (active component of Ozempic) have shown promise in the treatment of obesity for their regulation of appetite and reward processing. Importantly, the role of GLP-1 receptor agonists (GLP-1RAs) in reward processing is not well understood. Preclinical research has shown that acute doses of GLP-1RAs reduce the reward value of palatable food and attenuate cue-induced food-seeking. Similar reports have emerged with decreased motivation for drugs of abuse and associated cues. Therefore, we hypothesized that chronic GLP-1 administration reduces the incentive motivational value of reward cues. We tested this by treating male and female Sprague Dawley rats with escalating doses of semaglutide (SEMA; 7-70 ug/kg, s.c.) or vehicle (VEH) over ten days and then a maintenance dose (70 ug/kg) for the duration of the experiment. This treatment regimen is akin to that used in humans and caused weight loss in female rats while attenuating weight gain in males. To assess the value attributed to a reward cue, rats were then exposed to a Pavlovian conditioned approach (PavCA) paradigm where they learned to associate a cue (lever) with a food reward. The cue-elicited conditioned response was then used to study the effects of chronic SEMA on both the attribution of incentive value to the reward cue (i.e., acquisition) and the expression of behavior after value had been attributed. While we did not observe an effect of SEMA on the acquisition or expression of a cue-elicited conditioned response, we found that, relative to VEH, SEMA enhanced the conditioned reinforcing properties of the reward-cue as well as the incentive

motivational value of the food. However, when rats were given ad-libitum access to the same food reward, SEMA rats consumed less than VEH rats. These results suggest that chronic SEMA may exert its effect by increasing the initial value of the reward and associated cue and in turn reduce subsequent motivation and food-seeking behavior.

**Disclosures:** D. Pereira: None. S.E. Chang: None. N.N. Morales: None. C.A. Turner: None. S.B. Flagel: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.15/GG14

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** Small Faculty Grant from the College of Liberal Arts

**Title:** Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, on the expression of methamphetamine preference in adolescent male and female rats

**Authors:** \*T. P. NGUYEN, C. YEAP, A. R. ZAVALA;  
California State Univ., Long Beach, CA

**Abstract:** The use of methamphetamine (METH) is particularly detrimental during adolescence, as initiating use early often results in less successful treatment outcomes later in life. Importantly, there are currently no treatments for stimulant use disorder that have received FDA approval. Previous studies have linked drugs that activate glucagon-like peptide-1 (GLP-1) receptors, such as liraglutide (an FDA-approved medication for diabetes), to a decrease in the rewarding effects of cocaine, heroin, and oxycodone. However, the role of activating GLP-1 receptors on METH reward has not been examined, nor has it been examined in adolescent rats. Thus, we investigated whether stimulating GLP-1 receptors with liraglutide decreases METH-seeking behavior in adolescent rats using the conditioned place preference (CPP) paradigm, an animal model of drug reward. On day 1, habituation, rats were confined to each side of a two-chamber CPP apparatus for 10 mins. On days 2-4, baseline, rats had free access to both sides of the two-chamber apparatus for 30 min to determine their non-preferred side. During days 5-12, conditioning, rats were injected on alternating days with METH (0.0, 0.125, or 0.5 mg/kg, intraperitoneally) or saline and were immediately confined to their non-preferred and preferred side of the apparatus for 30 min, respectively. On day 14, testing 1, rats were pretreated with liraglutide (0.0 or 0.3 ug/kg, subcutaneously) 1 h before having free access to both sides of the apparatus for 30 min. A second test day occurred on day 16, during which the rats had free access to both sides of the apparatus in a drug-free state for 30 min. Preliminary results indicate that rats exhibit METH preference for the 0.5 mg dose of METH, and that the preference is attenuated with pretreatment with liraglutide. When considered together, these results will

elucidate a better understanding of the effects of METH in adolescents and highlight GLP-1 as a potential pharmacological target for the treatment of METH use disorder.

**Disclosures:** T.P. Nguyen: None. C. Yeap: None. A.R. Zavala: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.16/GG15

**Topic:** G.03. Stress and the Brain

**Title:** Circadian phase and biological sex are not major modifiers of stress-alcohol behavioral cross-sensitization in CFW mice

**Authors:** \*S. M. LOPEZ<sup>1</sup>, K. K. SZUMLINSKI<sup>2</sup>, J. CHI<sup>2</sup>, J. ISPASOIU<sup>2</sup>, W. LE<sup>2</sup>, A. LIANG<sup>2</sup>, A. NEI<sup>2</sup>, N. SAMAAN<sup>2</sup>, M. SHANKARRAM<sup>2</sup>, A. ZIMMERER<sup>2</sup>;

<sup>1</sup>UC, Santa Barbara, Santa Barbara, CA; <sup>2</sup>Psychological and Brain Sci., Univ. California-Santa Barbara, Santa Barbara, CA

**Abstract:** Nearly 29 million people reported having an alcohol use disorder (AUD) in the U.S. alone. Although males have higher rates of AUD, the diagnosis in females has increased over the past 10 years, which is concerning as females telescope through AUD more rapidly than males. Problematic drinking in females has been attributed to coping with stress and negative affect regulation. While repeated unpredictable stress has been well-characterized to influence AUD-related behaviors in male laboratory rodents, studies investigating stress-alcohol interactions in female subjects are lacking. Based on clinical and preclinical evidence that the propensity to drink is inversely related to alcohol behavioral sensitivity, we employed an 11-day repeated, unpredictable, mild stress (RUMS) procedure in CFW mice to examine for sex differences in stress-alcohol behavioral cross-sensitization and how that might be influenced by circadian phase. RUMS during the active/dark phase, but not during the inactive/light phase, lowered body weight in both females and males, with effects observed earlier in female subjects. Irrespective of phase, RUMS increased alcohol-induced locomotion and reduced the latency to right in both females and males. These data indicate negligible effects of circadian phase or biological sex on the capacity of RUMS to increase the motor-stimulating effects of alcohol, arguing against a major role for the organizational or activational effects of sex hormones in this phenomenon.

**Disclosures:** S.M. Lopez: None. K.K. Szumlinski: None. J. Chi: None. J. Ispasoiu: None. W. Le: None. A. Liang: None. A. Nei: None. N. Samaan: None. M. Shankarram: None. A. Zimmerer: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.17/HH1

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** NIMHR01106972

**Title:** Early-life adversity in rats alters the regulation of reward-seeking by reward-paired cues in sex-specific and process-specific manners.

**Authors:** \*B. HALBOUT<sup>1</sup>, S. B. OSTLUND<sup>2</sup>;

<sup>1</sup>California State University, Long Beach, Long Beach, CA; <sup>2</sup>Anesthesiol. and Perioperative Care, Univ. of California, Irvine, Irvine, CA

**Abstract:** Early-life adversity (ELA) is associated with higher risk for poor cognitive and emotional health during adulthood and increased susceptibility for mood- and reward-related disorders such as depressive and substance use disorders. Rodent models of ELA have exposed deficits in reward-related processes that are thought to contribute to these disorders. Despite important progress on this front, the scope and nature of reward processing dysfunction resulting from ELA remains insufficiently understood. Importantly, few studies have investigated how ELA affects cue-motivated reward seeking behavior. Reward-paired cues can play distinct roles in shaping behaviors, notably by exerting: 1) a motivating role through a *bottom-up* signal that energizes reward-seeking, 2) a controlling role through cognitive processes that can: *a-* regulate the impulse to engage in exploratory reward-seeking behaviors through a *top-down* regulation of motivation, or *b-* guide behavior in a goal-directed manner by signaling information about the nature of the reward predicted. We hypothesize that ELA might lead to abnormal cue-motivated behavior by disrupting *top-down* cognitive control processes, and this independently of potential impairment in motivation. **Methods:** We use a recently developed probabilistic Pavlovian-instrumental transfer (pPIT) task to determine the effects of ELA (limited bedding and nesting (LBN) procedure during postnatal days 2-9 vs. control (CTL) condition) on cue-elicited motivation and its cognitive control in female and male adult Long-Evans rats. We also use the well establish outcome specific PIT task (osPIT) to assess the ability of distinct cues to guide actions based on specific cue-reward associations. **Results:** In the pPIT, ELA disrupted the modulatory influences of reward-paired cues on reward seeking in a sex-specific manner. More specifically, the controlling influence of a cue associated with high probability of reward availability was enhanced in ELA exposed female rats while it was slightly attenuated in ELA male rats. The motivational influence of a cue paired with a low probability of reward was unaffected by ELA. Similarly, ELA did not alter the ability of reward-paired cues to enhance reward seeking responses directed to the specific rewards they predicted. **Conclusions:** ELA causes sex-specific alterations in the *top-down* regulation of reward-seeking by reward-paired cues, which might interfere with adaptive reward processing.

**Disclosures:** B. Halbout: None. S.B. Ostlund: None.

**Poster**



## **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.18/HH2

**Topic:** H.06. Anxiety Disorders

**Title:** The Role of Parvalbumin Interneurons and Perineuronal Nets in Prefrontal Cortex Following Learned Helplessness

**Authors:** \*L. AZIZ<sup>1</sup>, A. MANGANARO<sup>2</sup>, D. DUMITRIU<sup>1</sup>;

<sup>1</sup>Columbia Univ. Irving Med. Ctr., New York, NY; <sup>2</sup>Pediatric/Psychiatry, Columbia Univ. Irving Med. Ctr., New York City, NY

**Abstract:** This study investigated learned helplessness (LH), an animal model of repetitive aversive stressor-induced depressive-like behavior. After exposure to uncontrollable foot-shock (days 1-2), about 20% of animals exhibit passive-escape behavior on day 3—when escape from shock becomes possible—reflecting a “helpless” state, while the rest show active-escape behavior, reflecting a “resilient” phenotype, similarly to control mice not previously exposed to shock. Here, we focused on the role of parvalbumin (PV) interneurons and perineuronal nets (PNNs) in the medial prefrontal cortex (mPFC), a key area for regulating stress responses. Using TRAP2 × Ai14 transgenic mice, we permanently labeled neurons activated during LH day 3. Post-mortem brain sections from helpless, resilient, and control groups were analyzed via immunohistochemistry to quantify PV interneuron and PNN expression. Our results showed that helpless animals presented significantly lower PV<sup>+</sup> interneuron and PNN<sup>+</sup> cell density across the mPFC compared to control and resilient mice. TRAP-based activity mapping further revealed diminished recruitment of active PV<sup>+</sup> neurons in helpless animals during stress exposure, whereas resilient animals preserved both PV<sup>+</sup> density and activation. Preliminary colocalization analyses suggested fewer PV<sup>+</sup> neurons enwrapped by PNNs in helpless animals, with potential differences in the proportion of activated PV<sup>+</sup> cells expressing PNNs. These findings suggest that while helplessness is characterized by impaired inhibitory drive and limited plasticity, resilience involves the preservation of structural integrity and the dynamic recruitment of PV<sup>+</sup>PNN<sup>+</sup> networks within the medial prefrontal cortex.

**Disclosures:** L. Aziz: None. A. Manganaro: None. D. Dumitriu: None.

### **Poster**

## **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.19/HH3

**Topic:** H.06. Anxiety Disorders

**Title:** Brain-wide functional connectivity of PFC in Learned Helplessness

**Authors:** \*A. MANGANARO<sup>1</sup>, D. DUMITRIU<sup>2</sup>;

<sup>1</sup>Pediatrics/Psychiatry, Columbia Univ., New York City, NY; <sup>2</sup>Pediatrics/Psychiatry, Columbia Univ., New York, NY

**Abstract:** Pervasive or recurring negative experiences can induce a state of learned helplessness (LH), where individuals lose the sense of control over their environment, leading to maladaptive coping and emotional dysfunction. On the other hand, the ability to maintain an active response and not generalize in presence of a stressor is linked to resilience and better psychological outcomes. In an LH mouse model of active avoidance following repetitive uncontrollable stress, we found that inhibition of specific prefrontal cortex (PFC) pathways modulating helplessness led to divergent behavioral responses in relation to the paradigm contingencies. Surprisingly, we found that chemogenetic inhibition of PFC→BLA resulted in less helplessness during the escape avoidance session, presumably due to circuit plasticity occurring between training and testing sessions. Prior studies support the notion that PFC activity can regulate opposing changes in defensive behavior by recruiting distinct neuronal subpopulation in the downstream target region. Together, preliminary data suggest complex temporal dynamics in development of aberrant PFC activity associated with emergence and expression of helplessness. To investigate mechanisms underlying the role of PFC in LH, we adopt a macroscale approach to map wide-brain functional connectivity at two-time points of interest by using the single-cell resolution of the Fos gene expression captured by the TRAP2 system at first exposure to shock stressor, and the timed cFos staining at escape avoidance session. Specifically, we tracked the PFC activity changes and potential signs of plasticity of circuits in the single individual, to enhance our understanding of the dynamics following repetitive aversive stress. Findings from this research may provide new insights into the neural circuits that underlie stress-related disorders such as depression and anxiety.

**Disclosures:** A. Manganaro: None. D. Dumitriu: None.

**Poster**

**PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.20/HH4

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** Utah State University Office of Research

**Title:** Investigating the oxytocin system in the molecular basis of self-control

**Authors:** \*M. WACHTEL<sup>1</sup>, S. MAHMOUDI<sup>2</sup>, S. M. FREEMAN<sup>1</sup>;

<sup>1</sup>Biol., <sup>2</sup>Psychology, Utah State Univ., Logan, UT

**Abstract:** Oxytocin (OXT) is well-known for its role in regulating social behaviors such as pair-bonding, maternal care, and social motivation. At the core of these social behaviors is reward. OXT receptors (OXTR) are well-characterized in dopaminergic (DA) areas of the mesolimbocortical reward pathway in rodents, especially in the nucleus accumbens (NAc). We hypothesized that OXTR density in the NAc would be related to differences in impulsive behavior in rats, as measured by a delay-discounting task. Male (n=18) and female (n=24) Long Evans rats were assigned to either a truly random control (TRC) group or an unpaired (UN) group in a delay-discounting task. The TRC group was used in place of colony controls to account for any effects of behavioral testing. The UN group underwent a typical delay discounting test in which they were asked to choose between a smaller, sooner reward (SSR) and a larger, later reward (LLR). Rats underwent behavioral testing until behavioral choices were consistent between testing sessions; rats from the UN group were then divided into an impulsive group and self-controlled group based on the number of LLR choices in a 32-trial session; >50% selection of the LLR was the cutoff for the self-controlled group. Following completion of behavioral assays, all rats were euthanized via carbon dioxide inhalation. Brains were promptly removed and snap frozen. Brains were stored at -80C and cryosectioned at 20 um. Sections were thaw-mounted to microscope slides, which were stored at -80C until use in OXTR receptor autoradiography according to established methods. OXTR densities in the NAc from film autoradiograms were quantified using the MCID Core Digital Densitometry software. A two-way ANOVA was conducted to assess main effects of sex and behavioral group (impulsive, self-controlled, and TRC), as well as any interaction, on the density of OXTR in the NAc. We found no significant main effect of sex ( $F_{1,36}=0.687$ ;  $p=0.4126$ ;  $\eta^2=0.012$ ), but there was a significant main effect of behavioral group ( $F_{2,36}=10.87$ ;  $p=0.0002$ ;  $\eta^2=0.365$ ). Post-hoc tests revealed that self-controlled rats had significantly higher OXTR binding in the NAc compared to the other two groups; OXTR densities in the NAc of impulsive individuals did not differ from TRC. These findings suggest that elevated OXTR in the NAc is important in reward-based decision making. Delay discounting is a key feature in many impulsivity-related conditions, so our results have implications for OXT's potential role in addiction, in which the hedonic value of a substance has been inflated, and ADHD, where low motivation to begin effortful projects often leads to the selection of low effort, high reward behaviors.

**Disclosures:** M. Wachtel: None. S. Mahmoudi: None. S.M. Freeman: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.21/HH5

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** R16GM145552  
R25DA050687

**Title:** Vicarious defeat stress impairs spatial memory performance in female adolescent c57BL/6 mice.

**Authors:** \*A. THEMANN, S. D. INIGUEZ;  
Psychology, The Univ. of Texas at El Paso, El Paso, TX

**Abstract:** Exposure to psychological stress has been shown to increase the incidence of major depressive disorder, primarily in juvenile populations. Recently, our lab has established the vicarious defeat stress (VDS) paradigm for the study of psychological stress-induced depression-related behavior in vulnerable populations such as adolescents and females. Thus, the goal of this study was to examine whether exposure to VDS, in adolescent female mice specifically, resulted in an impairment of spatial memory performance on a standard Morris water maze (MWM) task. Here, on postnatal day (PD)35 adolescent female mice witnessed the defeat bout of a male conspecific by a CD-1 male aggressor for 10 minutes across 10 consecutive days. Non-stressed control mice were handled daily and pair-housed in cages with a perforated plexiglass divider. Forty-eight hours after, mice were tested on spatial memory performance on the MWM (PD46-57). We found that adolescent female mice, independent of stress exposure, learned to find the location of the escape platform across the training trials. However, 24 hours after training, female mice exposed to VDS displayed increases in the latency to locate the escape platform, indicating impairment of spatial memory. Collectively, this preclinical study uncovered that VDS, in adolescent female mice, results in memory impairment, one of the key phenotypes exhibited by individuals suffering from major depression.

**Disclosures:** A. Themann: None. S.D. Iniguez: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.22/HH6

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** R16GM145552

**Title:** Vicarious defeat stress impairs spatial memory performance in male adolescent c57BL/6 mice

**Authors:** \*C. A. FRAUSTO, M. RODRIGUEZ, S. D. INIGUEZ;  
The Univ. of Texas at El Paso, El Paso, TX

**Abstract:** Psychological stress exposure is a prevailing risk factor for the development of mood-related illnesses. Despite the growing literature indicating that affective disorders can arise after a traumatic event is vicariously experienced, this relationship remains to be thoroughly examined in juveniles at the preclinical level. Thus, the objective of the current investigation is to assess whether the vicarious defeat stress paradigm - a model that dissociates psychological versus

physical stress - induces a depression-like phenotype in adolescent male and female mice. Adolescent (5-week-old) male c57BL/6 mice witnessed the social defeat bout of a male conspecific, by a larger CD1 aggressor, for 10 consecutive days. Twenty-four hours after the last stress exposure (postnatal day 45), separate groups of mice were tested in the social interaction or Morris water maze. When compared to same-sex non-stressed controls, male mice exposed to vicarious defeat stress exhibited a depressive-like phenotype, as inferred from decreases in social behavior and spatial memory deficits. Collectively, our data suggest that the vicarious defeat stress paradigm may be used to examine the etiology of psychological stress-induced mood-related phenotypes in the juvenile population.

**Disclosures:** C.A. Frausto: None. M. Rodriguez: None. S.D. Iniguez: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.23/HH7

**Topic:** H.06. Anxiety Disorders

**Support:** Department of Defense Grant, HT94252310156

**Title:** A novel neural basis for anorexia-like phenotypes

**Authors:** \*C. SU<sup>1</sup>, Y. XU<sup>2</sup>, Q. TONG<sup>3</sup>;

<sup>1</sup>UTHealth at Houston, Houston, TX; <sup>2</sup>IMM, Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; <sup>3</sup>IMM, Univ. of Texas Hlth. Sci. Center, Houston, Houston, TX

**Abstract:** Anorexia nervosa (AN) is an eating disorder characterized by voluntarily restricted food intake, low body weight, distorted body image, increased anxiety and physical activity. AN normally occurs in juveniles and teenagers and has a very high mortality rate in girls. However, the underlying neural basis of AN remains largely unknown. In the present study, we demonstrate that aberrant hyperactivity of neurons expressing steroidogenic factor 1 (SF1) and estrogen receptor- $\alpha$  (ER $\alpha$ ) within the ventromedial hypothalamus (VMH), a critical brain region implicated in satiety regulation, contributes to the development of AN-like phenotypes and sexual dimorphism. To selectively activate these neuronal populations, we bilaterally injected Cre-dependent AAV-Flex-NaChBac into the VMH of transgenic mice. Anxiety-related behaviors were assessed using the open field and light/dark box paradigms. Chronic activation of ER $\alpha$ +SF1 neurons, but not activation of ER $\alpha$  or SF1 neurons alone, in the VMH led to severe hypophagia, self-starvation, and eventual mortality, with female mice exhibiting accelerated lethality compared to males. Additionally, both sexes displayed increased anxiety-like behavior and locomotor hyperactivity upon neuronal activation. Notably, although the VMH is predominantly composed of glutamatergic neurons, conditional knockout experiments revealed that brain-derived neurotrophic factor (BDNF)—rather than glutamate—plays a central role in mediating the anorexic phenotype. Moreover, targeted overexpression of BDNF in ER $\alpha$ +SF1

neurons recapitulated key behavioral features, including reduced food intake, heightened anxiety, and increased locomotor activity, in both sexes, but without inducing lethality. Collectively, these findings identify ER $\alpha$ +SF1 neurons in the VMH as a critical neural substrate underlying AN-like behaviors, and suggest that sex-specific distribution of ER $\alpha$ -expressing neurons within the VMH may contribute to the sexual dimorphism in AN. Moreover, BDNF emerges as a potential therapeutic target for the treatment of AN.

**Disclosures:** C. Su: None. Y. Xu: None. Q. Tong: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.24/HH8

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** HRD-1826745  
EES-2204750  
SC2GM109811

**Title:** Persistent changes in serotonin transporter expression in the hippocampus and prefrontal cortex of adult male c57BL/6 mice following adolescent fluoxetine exposure

**Authors:** \*D. E. CALVO, M. RODRIGUEZ, A. THEMANN, C. A. FRAUSTO, S. D. INIGUEZ;  
Psychology, Univ. of Texas at El Paso, El Paso, TX

**Abstract:** Prescription rates of fluoxetine, the most dispensed selective serotonin reuptake inhibitor, have been rising among the juvenile population. Since adolescence is a critical developmental period in which the brain undergoes fine-tuning, chronic increases in serotonin levels may lead to long-term neurobiological changes in brain regions responsible for emotional regulation. Thus, using mice as a model system, we explored how adolescent fluoxetine exposure (AFE) would influence the expression of serotonin transporters (SERT) in the adult hippocampus and prefrontal cortex. Specifically, postnatal day (PD)-35 male C57BL/6 mice were administered with fluoxetine (250 mg/l in their drinking water) for 15 consecutive days (PD35-49). Three weeks later, when mice reached adulthood (PD70), bilateral hippocampus and prefrontal cortex were dissected and analyzed for SERT protein expression. We found that, when compared to controls, AFE-mice exhibited increased SERT protein expression in the hippocampus. In contrast, expression of SERTs was decreased in the prefrontal cortex of these mice. Our data suggest that AFE induces long-term region-specific changes in SERT expression. Collectively, this study demonstrates that persistent fluoxetine-induced neurobiological changes are evident in adulthood when exposed to this antidepressant medication during the adolescent stage of development.

**Disclosures:** D.E. Calvo: None. M. Rodriguez: None. A. Themann: None. C.A. Frausto: None. S.D. Iniguez: None.

**Poster**

**PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.25/Web Only

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** Seed funding

**Title:** Mitochondrial complex I in cholinergic interneurons and cognitive impairment

**Authors:** \*M. JODEIRI FARSHBAF<sup>1</sup>, R. DURAND-DE CUTTOLI<sup>2</sup>, S. O. BROWN<sup>2</sup>, J. L. ABLES<sup>3</sup>;

<sup>1</sup>Icahn Sch. of Med. at Mount Sinai, NEW YORK, NY; <sup>2</sup>Neurosci., <sup>3</sup>Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

**Abstract:** Diabetes is the most common endocrine disorder in the United States. People with diabetes are more likely to experience mental health problems and the comorbidity of diabetes and mental health issues is a major challenge for efficient treatment of either problem in patients. Impulsivity is one of the complex behavioral traits which has been reported as increasing in patients with diabetes. Impulsive behaviors are characteristic of attention-deficit hyperactivity disorder (ADHD) and substance use disorders. However, the molecular mechanism of impulsive behavior formation in diabetes is unknown. Diabetes negatively impacts cholinergic neurons in the brain. To examine these relationships, we used developed mouse models of diabetes in both sexes by using a modified multiple low dose streptozocin (STZ) protocol. We have transcriptionally profiled the CIN from NAc in this model and our results show that mitochondrial complex I (MCI) in CIN has the most significant change in both male and female mice after 6 weeks of sustained hyperglycemia, but interestingly, expression of MCI genes in CIN return to control levels after 12 weeks. We have found that cholinergic interneurons (CIN) in the nucleus accumbens (NAc) are susceptible to diabetic hyperglycemia. Our RNA-seq results show that mitochondrial metabolism is reprogrammed in CIN in the NAc in response to diabetes in a sex dependent manner. During different stages of hyperglycemia, the metabolism of carbohydrates and oxidation of lipids are changed in CIN in the NAc. We used operant conditioning tasks to understand how MCI change in CIN in the NAc influence reward-seeking behavior. We found impulsive-like behavior emerges weeks after onset of hyperglycemia and mitochondrial transcriptomic changes within CIN. In addition, our behavioral results show cognitive flexibility is impaired in diabetic mice during task-switching. These results display how diabetes impacts MCI expression in CIN in the NAc and represents in the form of cognitive impairment. Human studies showed MCI abundance in the brain correlates with the ability of task-switching in humans. This study shows MCI and mitochondrial metabolic pathways in CIN

in the NAc is mainly correlates with impulsive-behavior and cognitive impairment in diabetic mice.

**Disclosures:** M. Jodeiri Farshbaf: None. R. Durand-De Cuttoli: None. S.O. Brown: None. J.L. Ables: None.

## **Poster**

### **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.26/HH9

**Topic:** G.03. Stress and the Brain

**Support:** NIH-NCCIH T32 AT002688  
VA BLRD Merit Award 1I01BX006155  
DoD PRP HT9425-24-1-0775

**Title:** Neurotrauma induces REM sleep disturbances, alpha-synuclein-related immunohistopathology, and behavioral impairments in a Parkinson's Disease model

**Authors:** \*L. DOVEK<sup>1</sup>, C. J. TINSLEY<sup>1</sup>, K. MCDANIEL<sup>1</sup>, L. NUNGARAY<sup>1</sup>, M. J. CHURCHILL<sup>1</sup>, C. MOORE<sup>1</sup>, C. K. MESHUL<sup>1</sup>, V. K. UNNI<sup>1</sup>, G. SCOTT<sup>1</sup>, J. J. ILIFF<sup>2</sup>, J. E. ELLIOTT<sup>1</sup>, M. M. LIM<sup>1</sup>;

<sup>1</sup>Oregon Hlth. & Sci. Univ., Portland, OR; <sup>2</sup>Univ. of Washington, Seattle, WA

**Abstract:** Neurotrauma, including traumatic brain injury (TBI) and/or post-traumatic stress disorder (PTSD), often leads to persistent sleep disturbances and increased risk for neurodegeneration. REM sleep behavior disorder (RBD), marked by elevated muscle activity during REM sleep (RSWA), is more frequent following neurotrauma and is linked to later development of Parkinson's disease (PD) and related synucleinopathies. To model prodromal PD, we combined neurotrauma with a synucleinopathy-prone preclinical model expressing an alpha-synuclein protein with the A53T mutation fused to enhance green fluorescent protein. Our model combines single prolonged stress (SPS), controlled cortical impact (CCI), and pre-formed fibrils (PFFs) injections to accelerate pathology. Subjects receiving PFFs and neurotrauma exhibited PD-relevant phenotypes including impaired gait, cognition, and sleep, along with elevated phosphorylated  $\alpha$ -synuclein in brain tissue. This model captures key features of early synucleinopathy and provides a platform for testing disease-modifying therapies following neurotrauma.

**Disclosures:** L. Dovek: None. C.J. Tinsley: None. K. McDaniel: None. L. Nungaray: None. M.J. Churchill: None. C. Moore: None. C.K. Meshul: None. V.K. Unni: None. G. Scott: None. J.J. Iliff: None. J.E. Elliott: None. M.M. Lim: None.

## **Poster**



## **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.27/HH10

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** Small Faculty Grant from the College of Liberal Arts  
NIH Grant T34GM149378  
CSULB BUILD Program in the Office of Undergraduate Research Services

**Title:** Establishing an inherently aversive environment in a place preference paradigm in male and female Sprague-Dawley adolescent rats

**Authors:** \*C. H. NGUYEN, A. G. SEDILLO, T. E. FALCON, A. R. ZAVALA;  
California State Univ., Long Beach, CA

**Abstract:** Conditioned Place Preference (CPP) studies typically employ an unbiased apparatus, which allows for assessing the rewarding effects of psychostimulant drugs and drug-seeking behavior (i.e., spending more time in an environment previously associated with the drug). In the present study, we aimed to create a naturally aversive environment by illuminating one side of the apparatus with white LED lights to assess the persistence of drug-seeking behavior despite the environment's aversive nature. A two-chamber apparatus was modified so that one compartment had a solid black wall pattern and a perforated acrylic black floor with horizontal grooves, and the second compartment had a white wall patterned with small black dots and a perforated acrylic floor with round holes. The preference for these two compartments was then assessed for 10 consecutive days during 30 min sessions beginning on postnatal day (PD) 38. The apparatus was then modified so that the white and circle-patterned side was illuminated with white LED lights (350 lux), while the solid black patterned side was illuminated with red LED lights (20 lux). The preference under these two conditions was then examined across four additional days during 45 min sessions. The time spent in the two compartments across the initial 10 days revealed that male and female rats consistently preferred the solid black compartment to the white one with a circle-patterned design. During days 11-14, rats showed a strong aversion to the white illuminated compartment, despite an increase in the amount of time they were allowed to explore both compartments. Importantly, this avoidance of the white illuminated compartment was evident even if animals were initially confined to the white compartment during the first 10 days. By establishing this new behavioral assay, drug-seeking behavior can be examined using this apparatus to determine whether this behavior persists in an aversive compartment. This approach will enhance our ability to study the neurobiological underpinnings of addiction, given that in humans, substance use is characterized by continued use despite adverse consequences.

**Disclosures:** C.H. Nguyen: None. A.G. Sedillo: None. T.E. Falcon: None. A.R. Zavala: None.

**Poster**

## **PSTR237: Preclinical Models of Neuropsychiatric Disease**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.28/HH11

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Support:** University of Michigan Research Scouts Program OORRS033123

**Title:** The impact of "chronic" semaglutide (Ozempic®) treatment on cue- and drug-induced reinstatement of cocaine-seeking behavior

**Authors:** \*C. A. TURNER<sup>1</sup>, N. MORALES<sup>3</sup>, S. E. CHANG<sup>1</sup>, D. PEREIRA<sup>1</sup>, E. SUN<sup>1</sup>, S. B. FLAGEL<sup>2</sup>;

<sup>2</sup>Michigan Neurosci. Inst., <sup>1</sup>Univ. of Michigan, Ann Arbor, MI; <sup>3</sup>Univ. of Puerto Rico, Trujillo Alto, Puerto Rico

**Abstract:** Semaglutide, a glucagon-like-peptide-1 (GLP-1) receptor agonist, is the active ingredient in drugs like Ozempic®. Although primarily used for weight loss, patients have anecdotally reported reductions in addiction-related behaviors, and ongoing clinical trials are investigating this phenomenon. In support, pre-clinical studies in rodents have shown that the effects of GLP-1 receptor agonists can generalize to drug-taking and -seeking behaviors related to cocaine, opioids, and alcohol. However, most prior pre-clinical studies examined the effects of acute GLP-1 receptor agonist treatment on drug-taking and -seeking behaviors. Here, we used an escalating semaglutide (SEMA) treatment regimen akin to that used for humans to investigate the effects of "chronic" SEMA on drug-seeking behavior. We hypothesized that SEMA-treated animals would show reduced cue- and drug-induced reinstatement of cocaine-seeking behavior compared to VEH-treated controls. To test this hypothesis, male and female rats underwent 14 days of cocaine self-administration, followed by approximately 28 days of forced abstinence. Beginning five days into the abstinence period and continuing for the duration of the experiment, animals received daily subcutaneous (s.c.) injections of VEH or SEMA. SEMA injections started at a dose of 7 µg/kg and increased by 7 µg/kg daily over 10 days, reaching a final maintenance dose of 70 µg/kg. This treatment regimen significantly attenuated weight gain in male rats, with pronounced weight loss in females. We then evaluated the reinstatement of cocaine-seeking behavior. Preliminary data suggests that SEMA treatment enhances cue-induced reinstatement relative to those treated with VEH. Conversely, SEMA treatment attenuates drug-induced reinstatement relative to those treated with VEH. Importantly, the drug-induced effects appear to be driven by differences in the sensitivity to cocaine's psychomotor-activating effects, as SEMA-treated animals entered stereotypy at lower doses of cocaine compared to VEH-treated animals. These data suggest that GLP-1 agonists may enhance the incentive value of drug-associated cues while also increasing the "potency" of drugs of abuse, like cocaine. These findings highlight the complexity of the effects of GLP-1 receptor activation and support the need for further investigation into the associated behavioral changes and underlying neurobiological mechanisms.

**Disclosures:** C.A. Turner: None. N. Morales: None. S.E. Chang: None. D. Pereira: None. E. Sun: None. S.B. Flagel: None.

## Poster

### PSTR237: Preclinical Models of Neuropsychiatric Disease

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR237.29/HH12

**Topic:** H.02. Reward and Appetitive Learning and Memory

**Title:** Sex differences in adolescent diazepam exposure on reward-related memory and perineuronal nets

**Authors:** S. RUFFINO<sup>1</sup>, E. ORTIZ FISHMAN<sup>2</sup>, L. WILLIS<sup>2</sup>, J. XU<sup>5,3</sup>, S. BATES<sup>6</sup>, \***M. T. TONG**<sup>4</sup>;

<sup>1</sup>Texas A&M Univ., College Station, TX; <sup>2</sup>Neurosci., Macalester Col., St. Paul, MN; <sup>3</sup>Macalester Col., St Paul, MN; <sup>4</sup>Biol., Macalester Col., Saint Paul, MN; <sup>5</sup>Chongqing, ; <sup>6</sup>Psychology, CSU Chico, Chico, CA

**Abstract:** Benzodiazepines (BZD) are used to treat anxiety disorders. However, misuse of BZDs has increased in adolescents with females reporting more misuse than males. Additionally, users engage in polydrug use with opioids. Despite the prevalence of BZD use in adolescence, few preclinical studies have examined its ramifications for this age group. Even fewer have looked at the role of extracellular matrix in sex differences in drug-related memory consolidation. Adolescent male and female mice were group-housed and placed in one of three drug conditions, diazepam (DZP) low dose (1mg/kg), DZP high dose (2 mg/kg), and saline. Anxiety levels were measured using the elevated plus maze (EPM) after drug or vehicle exposure. A conditioned place preference (CPP) paradigm was used to examine the rewarding effects of DZP. Also, we measured somatic withdrawal symptoms after exposure to naloxone. We used immunohistochemistry (IHC) to investigate perineuronal net (PNN) number and distribution in the hippocampus (HPC) and nucleus accumbens (NAc). We examine the co-localization of PNNs with medium spiny neurons in the NAc as well as neurons expressing L-type voltage-gated Ca<sup>2+</sup> channels (VGCCs) which are critical for LTP at the HPC-NAc synapse in females, but not males. Our results suggest that DZP at both doses (1 & 2 mg/kg) produce a significant place preference in males, but only the higher dose (2 mg/kg) produces a preference in females. This represents a rightward shift in females. Chronic DZP exposure only reduced anxiety-like behaviors in males. Furthermore, withdrawal from DZP increased anxiety-like behaviors in both sexes. However, DZP exposure reduces naloxone-precipitated withdrawal symptoms in both males and females. These results suggest that adolescents may be vulnerable to DZP abuse, with a heightened vulnerability in males. For our IHC experiments, we predict a dosage by sex interaction for PNN density around NAc MSNs after DZP exposure, and increased L-type VGCC reactivity following exposure compared to males. DZP induced reward-related place memory and attenuated opioid-withdrawal symptoms in adolescent male and female mice. However, female mice required a higher dose of DZP to form reward-related place memories, and chronic DZP only reduced anxiety-like behaviors in males. The findings suggest that the HPC-NAc-VTA circuit in females is less plastic overall which strongly implicates the role of PNNs as a main mechanism for sex differences observed. These findings should be of interest to

clinicians who prescribe benzodiazepines, as well as the scientific community interested in the role of the extracellular matrix in reward-related plasticity.

**Disclosures:** S. Ruffino: None. E. Ortiz Fishman: None. L. Willis: None. J. Xu: None. S. Bates: None. M.T. Tong: None.

## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.01/HH13

**Topic:** H.05. Mood Disorders

**Support:** JST SPRING, Grant Number, JPMJSP2145  
Tamura Science & Technology Foundation  
KAKENHI No, 23H04673  
KAKENHI No, 25H01727

**Title:** Alteration of locomotion and licking in paclitaxel-induced neuropathic pain model mice during goal-directed behavior

**Authors:** \*T. OTSUKI<sup>1,2</sup>, J. JUNQUEIRA<sup>1</sup>, J. MATSUMOTO<sup>1,3</sup>, T. SETOGAWA<sup>1,3</sup>, D. UTA<sup>4</sup>, H. NISHIMARU<sup>1,3</sup>;

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**Abstract:** Paclitaxel (PTX) is widely used in chemotherapy for common cancers such as breast cancers, but chronic peripheral-neuropathic-pain with subsequent depression and anxiety, accompanied by motivation deficits are known as its side effects. PTX-induced neuropathic pain (PiP) mice commonly used to elucidate its pathological mechanism exhibit mechanical hypersensitivity, as well as depression- and anxiety-like behaviors. However, it remains unclear whether this animal model shows deficits in motivated behaviors. To address this issue, we investigated changes in locomotion and licking behavior, both of which closely associated with goal-directed behavior, during an operant conditioning task used in standard laboratory experiments. Water-restricted mice were head-fixed on a polystyrene disc and trained to initiate spontaneous running to trigger a trial. After running for 1 second, a water drop was delivered as a reward, followed by a 2-second quiescence period. Trained mice were randomly assigned to either the sham group (n = 8) or the PiP group (n = 8) and the task performances were examined for 4 weeks. PiP mice exhibit mechanical hypersensitivity examined by von Frey test within the 1<sup>st</sup> week after injection, persisting until the 4<sup>th</sup> week. Changes in behavioral parameters during the task in PiP mice appeared from the 2<sup>nd</sup> week. Initially, the task success rate significantly declined. Subsequently, from the 3<sup>rd</sup> week, both the frequency of anticipatory licking and the locomotor speed toward the reward decreased in PiP mice compared with the sham group.

Moreover, frequency of anticipatory licking in PiP mice decreased after unrewarded trial compared with the rewarded trial indicating that low task performance affected the reward expectation in these mice. These results suggest that persistent pain in PiP mice reduces both reward-related motivation and expectation. The operant conditioning task employed in this study could be useful to elucidate the neuropathological mechanisms of motivation deficits in PiP mice. This work was supported by JST SPRING, Grant Number, JPMJSP2145 (TO), Tamura Science & Technology Foundation (HN), KAKENHI No, 23H04673 and 25H01727 (HN).

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## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.02/HH14

**Topic:** H.05. Mood Disorders

**Support:** 112-2320-B-002-035-MY3

**Title:** Chronic Haloperidol-Induced Supersensitivity to Amphetamine Challenge in Mice

**Authors:** \*C.-H. WU<sup>1</sup>, C. NG<sup>1</sup>, L.-J. LEE<sup>2</sup>;

<sup>2</sup>Anat. and Cell Biol., <sup>1</sup>Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan

**Abstract:** Dopamine supersensitivity is a known consequence of prolonged antipsychotic treatment and is associated with adverse effects such as treatment resistance and dopamine supersensitivity psychosis in schizophrenia. However, the mechanisms underlying this phenomenon remain unclear. In this study, we used heterozygous Disrupted-in-Schizophrenia 1 (Disc1 Het) mutant mice, a genetic model relevant to schizophrenia, to examine the development of dopamine supersensitivity following chronic haloperidol (HAL) exposure. Female wild-type (WT) and Disc1 Het mice were administered HAL (0.5 mg/kg, intraperitoneally) once daily for 1, 2, 3, or 6 weeks. After each treatment duration, mice received an amphetamine (Amph; 2.5 mg/kg) challenge to assess locomotor activity as a behavioral readout of dopamine reactivity. Amph significantly increased locomotion in both genotypes, with Het mice showing a heightened response. Following three weeks of HAL and a 3-day washout, both WT and Het mice exhibited enhanced Amph-induced hyperlocomotion, indicative of dopamine supersensitivity. Interestingly, WT mice developed this response after two weeks of treatment, while Het mice required three weeks, suggesting a delayed onset in the genetically vulnerable group. These findings demonstrate that chronic HAL treatment induces dopamine supersensitivity in both WT and Disc1 Het mice, with genotype-dependent differences in onset. This study provides evidence that genetic risk factors, such as Disc1 mutation, may modulate the trajectory of antipsychotic-induced dopamine dysregulation. This model offers a valuable tool

for investigating the interaction between genetic vulnerability and antipsychotic exposure, with implications for developing more personalized treatment strategies in schizophrenia.

**Disclosures:** C. Wu: None. C. Ng: None. L. Lee: None.

## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.03/HH15

**Topic:** H.05. Mood Disorders

**Support:** NIDA R15 DA058910

**Title:** Sex differences in activity-based anorexia development in adolescent mice

**Authors:** \*L. CONNOLLY<sup>1</sup>, H. THOMPSON<sup>1</sup>, A. K. RADKE<sup>2</sup>;

<sup>2</sup>Psychology, <sup>1</sup>Miami Univ., Oxford, OH

**Abstract:** Anorexia nervosa (AN) is a psychiatric disorder involving self-starvation and compulsive hyperactivity, resulting in severe weight loss, high relapse rates, and an elevated mortality rate. The activity-based anorexia (ABA) paradigm in rodents reflects key AN behaviors by combining limited food access and unrestricted running wheel access. While the ABA model has been widely applied in rats, its use in C57BL/6J mice is less common, with prior studies mainly focusing on females. Though AN is more prevalent in females during adolescence, males are also susceptible and studying both sexes is important for understanding sex-specific variations in AN behaviors and mechanisms. Therefore, this study examined sex differences in activity patterns, body weight, and food intake in adolescent C57BL/6J mice undergoing the ABA paradigm. From postnatal day (PND) 33 to 35, mice were randomly assigned to ABA or exercise control (EXE) groups, with all mice being acclimated to single cage housing, running wheels, and a reversed light/dark cycle. Starting on PND 36, ABA mice received food for the first 2 hours of the dark cycle, while the EXE mice had ad libitum food access. After feeding, all mice were moved to new cages to ensure food restriction for the ABA mice. All mice had continuous access to a running wheel and water. ABA mice were removed from the study when they lost 25% of their baseline body weight, adjusted for expected C57BL/6J adolescent growth (+0.15 g/day). EXE mice were removed when the last ABA mouse in the cohort was removed. Compared to EXE mice, ABA mice exhibited rapid weight loss despite the two groups having similar food intake, with females reaching criterion more quickly than males. ABA mice also showed greater total running activity, with females running more than males. However, both sexes displayed similar trends in food anticipatory activity (FAA), eating period activity, and post-prandial activity (PPA). FAA, occurring during the mice's inactive phase, was greater in ABA mice, while eating period activity, occurring during the mice's active phase, was greater in EXE mice. Together, results suggest that food restriction and alterations in activity timing contribute to the development of AN behaviors in both male and

female adolescent C57BL/6J mice, with females showing greater susceptibility to the ABA paradigm. These results lay the foundation for investigating the neurobiological mechanisms underlying AN behaviors. Given the role of mu-opioid receptor (MOR) signaling in the mesolimbic dopamine system in addictive behaviors, ongoing research will use transgenic mice lacking MORs to examine their role in modulating the behaviors observed in the ABA paradigm.

**Disclosures:** L. Connolly: None. H. Thompson: None. A.K. Radke: None.

## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.04/II1

**Topic:** H.05. Mood Disorders

**Support:** NIH Grant 1RF1AG082388-01

**Title:** Isoform-specific roles of neuronal GSK3 in neuropsychiatric behaviors in mice

**Authors:** \*N. SCHNEIDER<sup>1</sup>, N. I. NICOL<sup>1</sup>, H. M. JESTER<sup>1</sup>, N. SWIFT<sup>1</sup>, T. MA<sup>2</sup>;  
<sup>1</sup>Wake Forest Sch. of Med., Winston-Salem, NC; <sup>2</sup>Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC

**Abstract:** Glycogen synthase kinase 3 (GSK3) is a “master” kinase that is associated with numerous signaling pathways and an important regulator of many cellular functions. Given its wide range of function, the roles of GSK3 signaling have been investigated in the context of many organ systems and disease states, including psychiatric disease. For example, lithium, a widely used medication for treatment of bipolar disorder, is known to inhibit GSK3. Inhibition of GSK3 has also been trialed for neurologic diseases such as Alzheimer’s Disease, but with limited promise. Notably, GSK3 exists in two isoforms (GSK3 $\alpha$  and GSK3 $\beta$ ), and a majority of the studies focus on GSK3 $\beta$ . To the best of our knowledge, the isoform-specific roles of GSK3 in neuropsychiatric symptoms have not been reported. This study seeks to fill this critical knowledge gap by genetically suppressing the individual isoforms of GSK3 in neurons in mice and assessing for various potential neuropsychiatric phenotypes categorized within social motivation, anxiety-like, apathy-like, anhedonia-like, and despair-like paradigms at 3-5 months of age. We found that suppression of the GSK3 $\beta$ , but not the GSK3 $\alpha$  isoform, results in apathy-like behaviors (assessed by the marble burying test) when compared to control ( $p=0.001$  and  $p=0.94$ , respectively), with the GSK3 $\beta$  homozygous conditional knockout burying fewer marbles, a potential indicator of apathy. Surprisingly, no significant phenotypes were noted within the social motivation (assessed by 3-chamber test), anxiety-like (assessed by open field, elevated plus maze, and novelty induced hypophagia), anhedonia-like (assessed by sucrose preference test), or despair-like (assessed by forced swim test and tail suspension test) paradigms. A lack of other significant behavioral phenotypes seen in previous studies may suggest that suppression of only one isoform of GSK3 is insufficient to result in a phenotype due

to compensatory mechanisms of the intact isoform, or that the knockout of GSK3 in a neuron specific means may not be sufficient to result in behavioral changes.

**Disclosures:** N. Schneider: None. N.I. Nicol: None. H.M. Jester: None. N. Swift: None. T. Ma: None.

## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.05/II2

**Topic:** H.05. Mood Disorders

**Support:** Grant 202413-10 from Fundació La Marató de TV3 to MJG-F  
FPI\_022\_2022 predoctoral scholarship from CAIB to JJ-P  
Programa SOIB Recerca i Innovació (Progama INVESTIGO) program to FS-E

**Title:** Modeling Premenstrual Dysphoric Disorder in Sprague-Dawley Rats: A Preclinical Approach

**Authors:** \*J. JORNET-PLAZA<sup>1</sup>, F. SANSÓ-ELLE<sup>2</sup>, J. GARCIA-FUSTER<sup>3</sup>;  
<sup>2</sup>IUNICS, <sup>1</sup>Univ. of the Balearic Islands and IdISBa, Palma, Spain; <sup>3</sup>Med., IUNICS. Univ. of the Balearic Islands, Palma, Spain

**Abstract:** Premenstrual dysphoric disorder (PMDD) is a severe, hormone-related mood disorder that affects approximately 3-10% of women of reproductive age. It is characterized by affective and somatic symptoms—including depression, irritability, anxiety, and physical discomfort—and significantly impairs daily functioning and quality of life. Limited efficacy and adverse effects of existing treatments highlight the need for novel approaches. To support the development of new treatments, we aimed to validate a preclinical PMDD model in female Sprague-Dawley rats that replicates key behavioral and neuroendocrine features, enabling future translational research. To do so, a total of 31 adult female Sprague-Dawley rats were treated intraperitoneally with progesterone (500 µg, 1 ml/kg) once daily for either 5 days (n = 10) or 10 days (n = 12), while the control group received vehicle injections (1 ml/kg DMSO, n = 9). Following treatment, rats were exposed to forced drug withdrawal to simulate the abrupt decline in progesterone believed to contribute to the negative symptoms of PMDD. During withdrawal, rats were phenotype using a series of tests—including the forced-swim, open field, and sucrose preference—to assess various aspects of affective-like behavior. This procedure was also conducted in a separate group of 27 ovariectomized rats (vehicle n = 10; 5-day n = 8; 10-day n = 9). To confirm that surgeries were performed correctly, pre and post ovariectomy blood analysis revealed a significant decrease in progesterone levels ( $p < 0.0001$ ) through a ELISA kit. Data were analyzed using one-way ANOVAs, revealing only a significant effect for the sucrose preference test, indicating changes in hedonic-like responses. Specifically, Dunnett's *post-hoc*



comparisons showed dose-dependent reductions in sucrose preference among progesterone-treated rats (5 days:  $-18 \pm 13\%$ ,  $p = 0.285$ , n.s.; 10 days:  $-35 \pm 13\%$ ,  $*p = 0.020$ ) as compared to vehicle-treated controls. Similar effects were observed in ovariectomized female rats, with a decrease in the preference for sucrose after 10 days of progesterone ( $-37 \pm 12\%$ ,  $**p = 0.0076$  vs. control rats). These findings confirm that the prolonged progesterone exposure and subsequent withdrawal is associated with anhedonia as measured by decreased sucrose preference, offering a robust and relevant preclinical model of PMDD. Moreover, this anhedonic-like phenotype is independent of circulating sexual hormones as it is observed both in sham and ovariectomized rats. Thus, our PMDD preclinical paradigm is a valuable tool for assessing the efficacy of emerging therapeutic options targeting affective-like symptoms associated with the disorder.

**Disclosures:** J. Jornet-Plaza: None. F. Sansó-Elle: None. J. Garcia-Fuster: None.

## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.06/II3

**Topic:** H.05. Mood Disorders

**Title:** Chronic mild stress disrupts brain network coordination via neuroinflammatory and pro-apoptotic mechanisms

**Authors:** \*W. MA<sup>1,2</sup>, C.-C. LIU<sup>3</sup>, A. C.-W. HUANG<sup>2</sup>;

<sup>1</sup>Grad. Inst. of Life Sci., Natl. Def. Med. Ctr., Taipei City, Taiwan; <sup>2</sup>Psychology, Fo Guang Univ., Yilan County, Taiwan; <sup>3</sup>Grad. Inst. of Physiol., Natl. Def. Med. Univ., Taipei, Taiwan

**Abstract:** This study investigated how CMS disrupts brain-wide coordination of neuronal activity by analyzing inter-regional c-Fos correlations alongside cellular markers of inflammation and apoptosis. Eighteen male Sprague-Dawley rats were assigned to three groups: No CMS with PBS, CMS with PBS, and CMS with fluoxetine, and underwent a 28-day intervention. Behavioral assessments using the forced swim test, open field test, and novel object recognition test revealed that CMS increased immobility, reduced locomotor activity and exploration, and impaired recognition memory. Following behavioral testing, serum corticosterone and 5-HT levels were analyzed. c-Fos expression was used to compute inter-regional activity correlations across key brain areas including the medial prefrontal cortex, amygdala, and hippocampus. Immunohistochemical staining of IL-1 $\beta$  and Caspase-3 was performed to assess neuroinflammation and apoptosis. CMS rats exhibited elevated corticosterone and reduced 5-HT levels, indicating endocrine dysregulation. These systemic changes coincided with reduced c-Fos expression and elevated IL-1 $\beta$  and Caspase-3 across multiple regions, reflecting decreased neuronal activation, heightened inflammation, and enhanced apoptotic signaling; fluoxetine partially attenuated these IL-1 $\beta$  and Caspase-3 increases without fully normalizing them. Activity correlation mapping revealed altered coordination across brain regions involved in affective and cognitive processing. CMS reversed the positive

correlation between CA3 and DG, intensified negative coupling between CA2 and CA3, and weakened the link between PrL and BLA. In contrast, synchrony between CeA and CA1 increased abnormally, suggesting maladaptive emotional influence on memory circuits. These altered activity relationships paralleled region-specific inflammatory and apoptotic changes, suggesting a mechanistic link between tissue-level pathology and altered activity relationships. Together, these findings show that CMS-driven neuroinflammatory and pro-apoptotic changes interfere with inter-regional activity patterns and behavioral performance, shedding light on stress-related affective and cognitive disturbances.

**Disclosures:** W. Ma: None. C. Liu: None. A.C. Huang: None.

## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.07/Web Only

**Topic:** H.05. Mood Disorders

**Title:** The role of the lateral habenula in mediating Ketamine's antidepressant effects

**Authors:** Y. HU<sup>1</sup>, \*Y. LIU<sup>2</sup>;

<sup>1</sup>British Sch. of Bucharest, Voluntari, Romania; <sup>2</sup>INSTITUTE OF APICULTURAL RESEARCH, CSSA, Beijing, China

**Abstract:** Treatment-resistant depression (TRD) affects approximately 20%-30% of individuals with depression worldwide and poses a major clinical challenge due to the delayed onset, limited efficacy, and lack of sustained response to conventional monoamine-based antidepressants. Over the past two decades, ketamine has emerged as an alternative, demonstrating rapid and robust antidepressant effects in both clinical and preclinical studies. The Lateral Habenula (LHb), a crucial brain structure that is involved in encoding aversive stimuli and regulating mood-related behaviors, as a critical mediator of ketamine's antidepressant effects. This review summarizes recent progress in understanding how ketamine modulates LHb activity to exert its antidepressant effects. Electrophysiologically, depression models consistently reveal burst firing in LHb neurons, largely mediated by NMDA receptor activation and T-type calcium channel-driven low-threshold calcium spikes. Ketamine rapidly suppresses these aberrant firing by blocking LHb NMDA receptors and modulating T-type calcium channels, thereby restoring balanced neurotransmission in downstream monoaminergic circuits. At the molecular level, ketamine activates BDNF-TrkB pathway and calcium-dependent mechanisms, facilitating synaptic plasticity and long-term circuit remodeling. Moreover, the LHb exerts its influence through reciprocal connectivity with other mood-related brain regions, supporting ketamine's therapeutic effects via broader network-level modulation. We further highlight emerging directions for future research, including LHb-targeted circuit interventions, computational modeling of LHb dynamics, glial contributions to local regulation, and network-level interactions between the LHb and other brain regions that shape antidepressant outcomes.

**Disclosures:** Y. Hu: None. Y. Liu: None.

**Poster**

**PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.08/II4

**Topic:** H.05. Mood Disorders

**Title:** Psilocybin Demonstrates Robust Antidepressant Efficacy across Diverse Preclinical Models of Depression

**Authors:** Z. WANG, \*L. WANG, J. TAN;  
In Vivo Pharmacol. Unit, WuXi Biol., WuXi AppTec, Nantong, China

**Abstract:** Within the burgeoning realm of psychedelic research, psilocybin, along with its active metabolite psilocin, has emerged as a highly promising contender in the quest to discover innovative treatments for neuropsychiatric disorders. To this end, preclinical research utilizing animal disease models has yielded somewhat inconsistent findings when employing standard tests designed to evaluate depression - and anxiety - like behavioral phenotypes in response to psilocybin administration. This study evaluated the effects of psilocybin on several behavioral paradigms in two well-validated rodent models of depression. In the mouse chronic unpredictable mild stress (CUMS) model, a single high dose of psilocybin reversed depression-like behaviors in the open field test (OFT) and sucrose preference test (SPT). Moreover, a 21-day chronic administration of psilocybin (q.o.d.) improved mice performance in OFT, SPT, and elevated plus maze (EPM) in a similar pattern. Last but not least, psilocybin also exhibited significant antidepressant effects in the lipopolysaccharide (LPS)-induced inflammatory depression model in mice, restoring anxiety levels in OFT and hedonic responses in SPT. Our findings demonstrate that psilocybin's therapeutic potential transcends specific pathophysiological mechanisms, showing robust translational promise in both stress- and inflammation-driven rodent models of depression. The consistency of psilocybin's effects across acute/chronic dosing regimens and divergent etiological models underscores its broad-spectrum antidepressant capacity, supporting further clinical development for heterogeneous depression populations.

**Disclosures:** Z. Wang: A. Employment/Salary (full or part-time): WuXi AppTec. L. Wang: A. Employment/Salary (full or part-time): WuXi AppTec. J. Tan: A. Employment/Salary (full or part-time): WuXi AppTec.

**Poster**

**PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.09/II5

**Topic:** H.05. Mood Disorders

**Support:** KAKEN 22K07336  
KAKEN 22K07608  
KAKEN 22H02812  
KAKEN 18K07401  
ISHIBASHI FOUNDATION  
KAKEN 22K07569

**Title:** Cocaine Exposure Counteracts Antidepressant Effects of  $\Delta$ FosB and Electric Shock Preconditioning: Rescue via Chemogenetic Inhibition of VTA-NAc Dopaminergic Pathways

**Authors:** \*Y. N. OHNISHI<sup>1</sup>, Y. H. HONDA-OHNISHI<sup>2</sup>, Y. KAWAHARA<sup>4</sup>, A. NISHI<sup>3</sup>;  
<sup>1</sup>Dept. of pharmacology, Kurume Univ. Sch. of Med., Kurume, Japan; <sup>2</sup>Dept. of pharmacology, Kurume Univ. Sch. of Med., Fukuoka, Japan; <sup>3</sup>Dept. of Pharmacol., Kurume Univ. Sch. of Med., Kurume, Japan; <sup>4</sup>Dept. of pharmacology, Kurume Univ., Kurume, Japan

**Abstract:** Depression and cocaine use disorders frequently co-occur (~40% comorbidity), creating treatment-resistant conditions with poor clinical outcomes. While  $\Delta$ FosB accumulation in the nucleus accumbens (NAc) and electroconvulsive therapy (ECT) exhibit antidepressant-like effects, their vulnerability to cocaine exposure remains unexplored. Male C57BL/6J mice received bilateral NAc injections of AAV-expressing modified  $\Delta$ FosB (m $\Delta$ FosB) or underwent electric shock preconditioning (ECT protocol). Following chronic social defeat stress (10 days), mice underwent behavioral testing before and after cocaine administration (7.5 mg/kg  $\times$  4 days). For mechanistic studies, TH-Cre mice received retrograde AAV-DIO-hM4D(Gi) in NAc, allowing chemogenetic inhibition of VTA dopaminergic projections following administration of deschloroclozapine (DCZ). Despite robust initial stress resilience, both m $\Delta$ FosB-expressing mice and ECT-pretreated animals displayed profound social avoidance following cocaine exposure, comparable to non-resilient controls. This cocaine-induced exacerbation was specific to depression-like behaviors, as forced swim test immobility increased significantly only in stress-susceptible animals receiving cocaine, while anxiety measures remained unchanged. To investigate the underlying neural mechanisms, we are currently employing chemogenetic approaches using retrograde AAV-DIO-hM4D(Gi) to selectively inhibit VTA dopaminergic projections to the NAc. Preliminary results suggest that targeted inhibition of this pathway may rescue cocaine-induced exacerbation of depression-like behaviors. These findings reveal a critical vulnerability where cocaine exposure can override established antidepressant neuroadaptations, providing mechanistic insight into treatment resistance in comorbid conditions. Our ongoing chemogenetic studies will determine whether VTA-NAc dopaminergic transmission represents a viable therapeutic target for treating depression in the context of substance use disorders. This work establishes the first preclinical model demonstrating cocaine's ability to counteract established stress resilience mechanisms and identifies a novel therapeutic approach for addressing the challenging clinical comorbidity of depression and cocaine use disorders.

**Disclosures:** Y.N. Ohnishi: None. Y.H. Honda-Ohnishi: None. Y. Kawahara: None. A. Nishi: None.

**Poster**

**PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.10/II6

**Topic:** H.05. Mood Disorders

**Support:** Betty Huse Grant

**Title:** Sex-specific histone acetylation effects in adolescent depression

**Authors:** \*S. ZIMMERMAN;  
Univ. of Wisconsin-Milwaukee, Milwaukee, WI

**Abstract:** Mood disorders affect ~13% of adolescents in the USA, with a higher prevalence in females than in males. Adolescence is marked by a surge in gonadal hormone production, which may contribute to these sex differences. To test this hypothesis, we first examined sex differences in maladaptive behaviors following acute footshock stress in male and female mice. Stress induced social deficits and anxiety-like behavior, but no significant sex differences were observed during adolescence. Importantly, acute footshock stress during adulthood did not induce any maladaptive behaviors demonstrating that this stress vulnerability is specific to adolescence. Next, we conducted in silico systems bioinformatics using RNAseq data from the human prefrontal cortex. We found downregulation of KEGG steroid biosynthetic pathways in adolescents with depression. Interestingly, drug repurpose screening revealed that histone deacetylase (HDAC) inhibitors can reverse these observed molecular differences. In line with this, we identified that HDAC4 gene expression is upregulated along with specific acetylation changes on histone 2B and 3. Altogether, these findings suggest that decreased histone acetylation and/or increase HDAC activity may suppress steroid hormone synthesis during adolescence, potentially heightening the risk of depression. To validate these in silico findings, male and female mice received the HDAC inhibitor trichostatin A (TCA) prior to acute footshock stress and were tested for the development of maladaptive behaviors during adolescence. The same mice were allowed to reach adulthood and re-tested in the absence of stress and treatment to determine whether preventing acetylation changes during adolescence is prophylactic against development of maladaptive behaviors during adulthood. Preliminary results show that TCA reversed social deficits during adolescents and prevented development of anxiety-like deficits during adulthood. Sex differences may be present with female mice driving the effect; however, increased power is required to draw safe conclusions. TCA had no effect on social and anxiety-like behaviors in the absence of stress. These findings suggest that stress-induced decrease in acetylation may contribute to adolescent development of stress-related phenotypes due to downregulation of hormonal pathways. Moreover, our findings may provide new targets for intervention for the treatment of depression during adolescence.

**Disclosures:** S. Zimmerman: None.

**Poster**

**PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.11/II7

**Topic:** H.05. Mood Disorders

**Title:** Assessment of two chronic stress exposure protocols for the induction of depression-like changes in female C57BL/6J mice

**Authors:** R. IMMONEN, M. YACoub, D. F. DELOTTERIE, J. K. UHARI-VÄÄNÄNEN, T. HEIKKINEN, \*K. LEHTIMÄKI, **J. RYTKÖNEN**, S. BÄCK;  
Charles River Discovery Res. Services, Kuopio, Finland

**Abstract:** Depressive disorder, or depression, is a common mental disorder that has a strong effect on quality of life. Although there are effective treatments available, not all patients benefit from them. There is a clear need for new approaches and interventions for the treatment, management, and prevention of depression. To enable progress in this area, valid animal models are needed. Chronic models of depression in animals aim to replicate the long-term effects of stress on mood disorders. These models often involve exposing animals to repeated stressors, such as forced swimming, social defeat, or chronic mild stress, leading to changes in behavior, neurochemistry, and neuroendocrine function that resemble symptoms of depression in humans. In this study we compared two chronic stress mouse models that use repeated exposure to stress to replicate the long-term effects of stress on mood disorders.

The study was performed in adult female C57BL/6J mice. The animals were divided into three experimental groups (n=18/group), including one control groups and two groups exposed to stress. Starting from one week prior to the stress exposure, the animals in the cohorts exposed to stress were single-housed. One group was exposed to restraint stress by restriction of movement for a maximum of 4 hours per day for 5 weeks. The other group of animals followed a protocol of daily unpredictable stress exposure for a 5-week period. The effects of the long-term stress exposure were evaluated using behavioral assessment, including open field assessment, elevated plus maze test, sucrose preference test, contextual fear conditioning, force swim test, and tail suspension test. After completing the stress exposure protocols, the animals were subjected to dynamic functional ultrasound scans of their brains under ketamine-medetomidine anesthesia. Brain activation upon whisker stimulation and the vascular reactivity were assessed. During the entire experiment, the welfare of the animals was closely monitored, with any sign of welfare issue leading to halting the stressor and returning the animal to its home cage.

Chronic stress exposure induced changes in behavioral assays, suggesting that the models can be used to replicate the effects of long-term stress on mood disorders. The platforms can serve as tools in drug discovery pipelines aiming to identify novel treatments for mood disorders linked to chronic stress exposure.

**Disclosures:** **R. Immonen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **M. Yacoub:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **D.F. Delotterie:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **J.K. Uhari-Väänänen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **T. Heikkinen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **K. Lehtimäki:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **J. Rytönen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **S. Bäck:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services.

## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.12/II8

**Topic:** H.05. Mood Disorders

**Support:** NIMH T32  
UIC CCTS

**Title:** Unravelling the neuroendocrine-gut microbiota role in perinatal depression (PND); a microbiota gut-brain axis (MGBA) study in pregnancy utilizing a novel translational mouse model of PND

**Authors:** \***A. TRAN**<sup>1</sup>, M. E. RAGOZZINO<sup>2</sup>, B. PEÑALVER BERNABÉ<sup>1</sup>;  
<sup>2</sup>Psychology, <sup>1</sup>Univ. of Illinois Chicago, Chicago, IL

**Abstract:** Perinatal depression (PND) affects 12% of women in the US, most of whom do not receive adequate care. Given the high prevalence of untreated PND, uncovering a therapeutic is crucial for the health of pregnant women and their babies. The gut microbiome varies throughout pregnancy and its dysregulation is directly involved in major depressive disorder yet the gut-brain axis in PND remains to be understood. We designed a novel mouse model in which the mechanisms of PND via the gut-microbiota could be probed. In this study, stool from three 3<sup>rd</sup> trimester pregnant women with moderate-to-severe depression at the time of sample collection were combined for use as a fecal microbiota transplant (FMT) to germ-free (GF) mice. After three inoculations over 2 weeks, the humanized female mice were bred in trios with GF males for 8-11 days. Throughout the study, fecal samples were collected and a 5min behavioral test for depression, the splash test, was conducted 4 times. The splash test measures apathy with less grooming time indicative of more apathy. A mixed-effects model of the splash test yielded significant results. At session 1 all animals were GF and there was no significant difference in grooming time between HC and PND grouped mice. At session 2, after 2 rounds of FMT prior to breeding, there was a statistically significant difference, where the HC group grooming time was nearly unchanged at 163s and the PND group dropped to 125s. At session 3 after breeding, the

HC grooming time experienced a significant drop. At session 4 by the end of pregnancy, HC grooming times recovered. The PND grooming time remained low consistently from sessions 2:3 and 3:4. In summary, in HC animals, the induction of pregnancy increased apathy. However, by the end of pregnancy, the grooming behavior returned to pre-breeding levels in the HC mice, while the PND animals retained their increased apathy induced by the FMTs throughout the breeding and pregnancy periods. These results are the first to show that PND stool may be causal in conveying depression. We are further phenotyping our novel pregnancy model using additional behavioral tests and assessing multiple biological measurements, which are informing our understanding of the mechanisms underlying the dysregulated gut-brain axis in PND.

**Disclosures:** A. Tran: None. M.E. Ragozzino: None. B. Peñalver Bernabé: None.

## **Poster**

### **PSTR238: Mood Disorders: Behavior, Treatment, and Physiological Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR238.13/II9

**Topic:** H.04. Emotion

**Support:** JP23KJ1972  
grant from FUJIMIC, Inc. Tokyo

**Title:** The effect of inaudible ultrasound exposure on emotional states in olfactory bulbectomized rat depression model

**Authors:** \*T. YAMAUCHI<sup>1</sup>, D. YAMADA<sup>1</sup>, S. KASAI<sup>1,2</sup>, Y. NAKANO<sup>1,2</sup>, K. YOSHIKAWA<sup>1,2</sup>, S. NISHINO<sup>3</sup>, S. MIYAZAKI<sup>1</sup>, A. SAITOH<sup>1</sup>;  
<sup>1</sup>Tokyo Univ. of Sci., Katsushika-ku, Tokyo, Japan; <sup>2</sup>Pharm., Tokyo Univ. of Sci., Katsushika-ku, Japan; <sup>3</sup>Fujimic, Inc., Koto-ku, Tokyo, Japan

**Abstract:** [Introduction]Recently, inaudible ultrasound (US) exposure has been shown to be a non-invasive method for modulating brain activity. Previous human studies have shown that inaudible high-frequency components evoke various physiological, psychological, and behavioral responses. However, its underlying mechanisms remain unclear. In this study, we investigated the effects of the inaudible US exposure on depressive-like symptoms using an olfactory bulbectomized (OBX) rat depression model. [Methods]Male Wistar/ST rats were used. First, we examined the effects of US on auditory cognition in naïve rats. Rats were exposed to US for 60 min, after which the number of c-Fos-positive cells was evaluated. Moreover, to evaluate the effect of US from a behavioral assessment, we conducted an auditory fear conditioning test using 100 kHz US as the conditioned stimulus. OBX rats were used to evaluate the effect of US exposure on depressive-like symptoms. The OBX rat model was prepared by olfactory bulbectomy surgery and housed individually for 2 weeks. Thereafter, the OBX rats were exposed to artificial 100 kHz US. Hyperemotionality (HE) was evaluated as depressive-like behavior before and after ultrasound exposure, and plasma corticosterone and monoamine levels



were measured. [Results]In naïve rats, exposure to 100 kHz US did not affect the number of c-Fos-positive cells in auditory-related cortical areas. In addition, in the auditory fear conditioning test, the rats did not exhibit freezing behavior when 100kHz US was presented as a conditioned stimulus. These results suggested that 100 kHz US is inaudible to rats. Next, we investigated changes in emotional behaviors in an animal model of depression following exposure to US. The exposure to US significantly decreased the HE observed in OBX rats. Additionally, the plasma corticosterone levels in OBX rats were significantly reduced following US exposure. These changes were accompanied by alterations in serotonin metabolism in the anterior cingulate cortex (ACC). [Discussion]In this study, we found that 100 kHz US exposure could improve depressive-like behavior, even though the 100 kHz US used in this study is inaudible to rats. This behavioral change was accompanied by physiological changes, such as reduced corticosterone levels, and neurochemical changes, including altered serotonin metabolism. We propose that OBX rats should be an appropriate animal model for identifying the underlying mechanisms of emotional change following US exposure. Moreover, our results demonstrate that inaudible US can modulate the emotional state, suggesting its therapeutic potential against mood disorders such as depression.

**Disclosures:** **T. Yamauchi:** 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.; JSPS:JP23KJ1972. **D. Yamada:** None. **S. Kasai:** None. **Y. Nakano:** None. **K. Yoshizawa:** None. **A. Saitoh:** 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.; fund from Fujimic Inc..

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.01/II10

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH grant F32DA054767  
NIH grant R01DA035943

**Title:** Fentanyl reinforcement history has sex-specific effects on multi-step decision-making

**Authors:** \***E. GARR**, Y. CHENG, P. H. JANAK;  
Johns Hopkins Univ., Baltimore, MD

**Abstract:** It is commonly thought that drug addiction involves a transition to habitual control of action, where the choice to consume drugs becomes automatized and reflects a failure to deliberate over possible negative outcomes. Determining whether the pursuit of addictive drugs

is habitual is hampered by a lack of behavior assessments suitable for use during a bout of actual drug seeking. To understand how variable histories of drug reinforcement might affect goal-directed and habitual pursuit of drug, we trained rats ( $n = 35$ ) to perform a multi-step decision-making task to earn oral fentanyl and sucrose rewards following extensive pretraining with either fentanyl or sucrose. This task allowed for independent measurements of goal-directed and habitual choice characteristics during online pursuit of rewards, and habitual choice could be further categorized into perseverative and reward-guided components. Chronic fentanyl led to a bias for reward-guided habitual choice specifically in females (outcome  $\times$  transition  $\times$  group  $\times$  sex,  $p = .005$ ), and a high degree of perseveration in both sexes (main effect of group,  $p = .037$ ). Computational modelling recapitulated the bias for reward-guided habits in females exposed to chronic fentanyl (group  $\times$  sex  $\times$  agent,  $p = .047$ ), and also revealed that males exposed to chronic fentanyl showed an opposite bias away from reward-guided habits on a subset of trials (group  $\times$  sex  $\times$  state  $\times$  agent,  $p = .026$ ). These behavioral changes after chronic fentanyl pre-training generalized across fentanyl and sucrose seeking. In contrast, acute fentanyl selectively increased perseveration in females (sex  $\times$  reward,  $p = .019$ ), and blunted the gradual within-session improvement in goal-directed choice in both sexes (outcome  $\times$  transition  $\times$  reward  $\times$  session half,  $p = .047$ ). To investigate possible neural correlates underlying fentanyl-induced habits, a separate cohort of female rats ( $n = 7$ ) was given extensive pre-training on the decision-making task with sucrose reward, followed by fiber photometry recordings from neurons expressing the D2 dopamine receptor in the dorsomedial striatum during alternating sessions of sucrose and fentanyl. Calcium traces showed an ipsilateral bias, negative modulation during reward consumption, and side-specific reward prediction-error encoding, all of which were unaffected by fentanyl reward. Collectively, these results show that chronic fentanyl reinforcement promotes habits that generalize across drug and non-drug reward seeking, and that female rats are especially susceptible to habitual control induced by both chronic and acute fentanyl reinforcement.

**Disclosures:** E. Garr: None. Y. Cheng: None. P.H. Janak: None.

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.02/III1

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** Acadia Pharmaceuticals

**Title:** Pimavanserin attenuates precipitated morphine withdrawal syndrome and its aversiveness in rats.

**Authors:** \*P.-H. TSAI<sup>1</sup>, E. JONES<sup>1</sup>, H. QAMAR<sup>1</sup>, G. SAJI<sup>1</sup>, E. MORALES<sup>1</sup>, Y. REED<sup>1</sup>, C. P. WARD<sup>1</sup>, G. MORENO<sup>1</sup>, E. S. BURSTEIN<sup>2</sup>, D. H. MALIN<sup>1</sup>;

<sup>1</sup>Univ. of Houston-Clear Lake, Houston, TX; <sup>2</sup>Acadia Pharmaceuticals, San Diego, CA

**Abstract:** Experiments tested whether pimavanserin, a 5-HT<sub>2A</sub>R inverse agonist FDA approved for the treatment of hallucinations and delusions associated with Parkinson's Disease psychosis, would reduce somatically expressed signs of naloxone-precipitated withdrawal, as well as its aversiveness as indicated by conditioned place avoidance. Further experiments tested replicability of the effect on withdrawal signs and assessed pimavanserin effects in non-dependent rats. In Expt. A, SD male rats, averaging 301 g, were infused s.c. for 7 days with morphine sulfate. They were pretested for somatic withdrawal signs and for relative time spent in two compartments of different appearance during 15 min. free exploration of a conditioned preference apparatus. On day 6 of infusion, they were injected with saline alone, n = 9, or 1.3 mg/kg pimavanserin, n = 12. This was followed in 1 hr. by 0.3 mg/kg s.c. naloxone (NX). Then each rat was locked in one of the two compartments (which compartment was counterbalanced among rats) and scored over 20 min. under blind conditions on a standard checklist of opiate withdrawal signs. Changes from each rat's baseline signs were calculated. Compared with saline-injected rats, pimavanserin reduced the average increase from pretest in withdrawal signs by 41.4%. This difference was significant by t-test,  $p = .024$ . On the following day, rats were retested for compartment preference using the unbiased method under blind conditions. Saline-injected rats had a marked reduction of time spent in the withdrawal-associated compartment. This avoidance increase was reduced by 71.8% in the pimavanserin group,  $p = .021$ . Experiment B repeated Expt. A, except that all rats were infused with saline only. In both treatment groups, NX injections resulted in very small deviations from baseline scores. Compared with saline injections, pimavanserin induced no significant difference in NX-induced changes in somatic signs or in time spent in the NX-associated compartment. Experiment C repeated the Expt. A procedure for NX-precipitated somatically-expressed signs with the addition of a negative control group for withdrawal, saline-infused/saline-injected rats. As expected, the morphine-infused/saline injected group had significantly elevated increase in signs compared with negative controls,  $p < .001$ , by Tukey's HSD test for multiple non-independent comparisons. Compared with the morphine-infused/saline-injected rats, pimavanserin again reduced the increase in withdrawal signs, this time by 75.6%,  $p < .001$ . The results suggest that pimavanserin might alleviate some symptoms associated with morphine physical dependence.

**Disclosures:** P. Tsai: None. E. Jones: None. H. Qamar: None. G. Saji: None. E. Morales: None. Y. Reed: None. C.P. Ward: None. G. Moreno: None. E.S. Burstein: A. Employment/Salary (full or part-time): Acadia Pharmaceuticals. D.H. Malin: 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.; University of Houston-Clear Lake.

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.03/II12

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NSTC 113-2923-H-431 -001 -MY3  
NSTC 113-2811-H-431-001

**Title:** Footshock stress enhances reward and attenuates morphine-induced aversion: Behavioral and neural correlates

**Authors:** \*A. C.-W. HUANG<sup>1</sup>, Y.-C. YU<sup>2</sup>, A. KOZLOWSKA<sup>3</sup>, C. WU<sup>4</sup>, C.-N. CHENG<sup>2</sup>;  
<sup>1</sup>Fo Guang Univ, Psychology, Yilan County, Taiwan; <sup>2</sup>Psychology, Fo Guang Univ., Yilan County, Taiwan; <sup>3</sup>Dept. of Human Physiol. and Pathophysiology, Collegium Medicum, Univ. of Warmia and Mazury, Olsztyn, Poland; <sup>4</sup>Keelung Hosp., Keelung, Taiwan

**Abstract:** The influence of stress on the behaviors and neural substrates underlying opioid use disorder (OUD) remains unclear. To address this issue, a rat model combining morphine administration with footshock stress was used in the study. During the initial experiment, all rats were subjected to 10-second footshock (3 mA) treatments. Subsequently, all rats to drink a 0.1% saccharin solution for 15 minutes before intraperitoneal injection with normal saline or 20 mg/kg of morphine to form conditioned taste aversion (CTA). Next, rats were placed in a conditioned place preference (CPP) compartment for 30 minutes to induce CPP learning. The results showed that morphine simultaneously induced aversion in the CTA and reward in the CPP. Footshock stress blunted morphine-induced aversion in the CTA and enhanced morphine-induced reward in the CPP task. c-Fos expression was fewer in the basolateral amygdala (BLA) under morphine administration and hyperactive in the PrL and IL under footshock stress. Combined footshock stress and morphine injections increased c-Fos expression in the prelimbic cortex (PrL), infralimbic cortex (IL), and BLA. Footshock stress appeared to disrupt the correlations among the cingulate cortex 1 (Cg1), prelimbic cortex (PrL), infralimbic cortex (IL), nucleus accumbens (NAc), and basolateral amygdala (BLA). The network data indicated that footshock stress enhanced addiction-related neural pathways for the NAc and the PrL, IL, and BLA after morphine administration. The findings extend the paradoxical hypothesis of abused drugs and provide clinical contributions to the literature on OUD.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.04/II13

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** JP19mk0101156  
24K18291

**Title:** A preclinical strategy for evaluating opioid abuse-deterrent formulations combining antagonists

**Authors:** \*X. ZHANG<sup>1</sup>, T. NAGAI<sup>2</sup>;

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**Abstract:** Opioids are commonly used as narcotic analgesics in clinical settings. The misuse and addiction to opioid analgesia has been increasing in the United States of America and other countries. Therefore, the development of abuse-deterrent formulations has become an urgent issue. Major efforts have been made to mitigate this public health crisis. For instance, abuse-deterrent opioids with physical or chemical barriers have been developed to increase the difficulty of crushing or dissolving drugs. Abuse-deterrent opioids containing an opioid receptor antagonist have been shown to inhibit the rewarding effects of drugs. The effectiveness of the physical or chemical barrier formulation can be evaluated through dissolution testing. However, there is currently no established method for validating formulations with an opioid receptor antagonist in the preclinical phase. In this study, we validated the abuse-deterrent opioids containing the opioid receptor antagonist naloxone using the conditioned place preference (CPP) test. The study found that morphine (30  $\mu\text{mol/kg}$ ), oxycodone (3  $\mu\text{mol/kg}$ ), fentanyl (0.4  $\mu\text{mol/kg}$ ), and buprenorphine (0.5  $\mu\text{mol/kg}$ ) induced place preference in mice. The optimal ratio of naloxone and opioids to inhibit the rewarding effects of the latter was also examined. Naloxone (3-5  $\mu\text{mol/kg}$ ) effectively inhibited place preference induced by the opioids tested. The study calculated theoretical drug doses based on two parameters:  $\mu$ -opioid receptor binding affinity and blood-brain barrier permeability, which exerted the same pharmacodynamic effects. The theoretical doses were found to be very close to the drug doses at which mice showed place preference. Therefore, the CPP test is a useful behavioral method for evaluating abuse-deterrent formulations of opioids mixed with an antagonist. The ratio of naloxone to opioids, at which mice did not show a preference for a conditioned place, may serve as an effective index for developing abuse-deterrent formulations. Ratios can be calculated for other opioids based on their  $\mu$ -opioid receptor binding affinity and blood-brain barrier permeability.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

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**Program #/Poster #:** PSTR239.05/II14

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH Grant AA029674

**Title:** Targeting glutamate transport with novel beta-lactam GLT1 enhancer, MC-100093, in C57BL/6 mouse model of opioid overdose

**Authors:** W. WONG<sup>1</sup>, W. E. CHILDERS, Jr.<sup>2</sup>, M. ABOU-GHARBIA<sup>2</sup>, \*Y. SARI, M<sup>3</sup>;  
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**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:107%; mso-pagination:widow-orphan; font-size:11.0pt; 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-kerning:1.0pt; mso-ligatures:standardcontextual;} Chronic exposure and overdose of opioid cause respiratory depression and neurotoxicity through alterations of several neurotransmitters, including glutamate. Targeting glutamate transporter 1 (GLT-1) has been shown to attenuate the effects of chronic exposure to drugs of abuse, including opioids. In this study, the effects of GLT-1 enhancers (e.g. MC-100093 and ceftriaxone), were evaluated in C57BL/6 mice exposed to hydrocodone overdose. Male C57BL/6 mice received hydrocodone (20 mg/kg, i.p.) every other day for 13 days, and then received a higher dose of hydrocodone (40 mg /kg, i.p.) on day 15. Control group received i.p. injection of saline every other day, and the mice in the treatment groups received MC-100093 (50 mg/kg, i.p.) or ceftriaxone (200 mg/kg, i.p.) during the last five days of the study. This study used comprehensive laboratory animal monitoring system (CLAMS) to measure mice's respiratory frequency, locomotor activity, O<sub>2</sub> consumption, and CO<sub>2</sub> production. Exposure to hydrocodone overdose increased O<sub>2</sub> consumption and CO<sub>2</sub> production, MC-100093 and ceftriaxone treatments attenuated these effects. Furthermore, hydrocodone overdose increased metabotropic glutamate receptor 1 (mGluR1) expression and decreased GLT-1 and cystine/glutamate antiporter (xCT) expression in the nucleus accumbens, amygdala, and dorsomedial prefrontal cortex. Hydrocodone overdose upregulated tumor necrosis factor-alpha (TNF- $\alpha$ ), and high mobility group box 1 (HMGB1) and decreased brain-derived neurotrophic factor (BDNF) in these brain regions. Importantly, MC-100093 and ceftriaxone attenuated hydrocodone-induced alterations of GLT-1, xCT, BDNF mGluR1, TNF- $\alpha$ , and HMGB1 expression in these brain regions. These findings suggest that the novel  $\beta$ -lactam, MC-100093, might attenuate some of the effects of opioid overdose.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.06/JJ1

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIDA P01DA047233  
NIDA R01DA007359

**Title:** Transcriptional and behavioral characterization of individual differences in escalating oral oxycodone self-administration

**Authors:** \***B. T. KIPP**<sup>1</sup>, T. M. GYLES<sup>3</sup>, L. HOLT<sup>2</sup>, V. KONDEV<sup>2</sup>, E. KAHN<sup>2</sup>, E. J. NESTLER<sup>3</sup>;

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**Abstract:** Opioid use disorder (OUD) continues to be a complex and burgeoning healthcare issue with an estimated annual cost greater than \$700 billion in 2018, and an increasing rate of overdose deaths in the years since. Prescription opioids have contributed to the ongoing opioid epidemic and remain a potent gateway drug in substance use disorders. Among prescription opioids, oxycodone has a greater abuse potential due to, in part, higher likeability scores and fewer adverse side effects compared to other opioids. Here, we sought to characterize a homecage prescription opioid abuse model by measuring behavioral and transcriptional changes following oral oxycodone self-administration. Singly housed adult male and female C57BL/6J mice were exposed to increasing oxycodone concentrations in drinking water prior to 14 days of 1 mg/mL oxycodone two-bottle choice or water (CON). A clustering-based approach was used to identify two subpopulations of oxycodone consuming mice, namely those that escalate their consumption (High Escalators - HE), versus those who maintain stable oxycodone consumption (Low Escalators - LE) throughout the paradigm. We then performed RNA sequencing on tissue from the prefrontal cortex (PFC) and nucleus accumbens (NAc), followed by Multiscale Embedded Gene Co-expression Network Analysis (MEGENA). This analysis revealed distinct, region-specific transcriptional networks that segregate with the HE and LE phenotypes. Moreover, HE mice demonstrate lasting behavioral differences in withdrawal at prolonged abstinence time points compared to LE mice, marked by increased oxycodone seeking and negative affective behaviors that resemble clinical presentation of opioid use disorder. In summary, this model recapitulates some of the essential features of opioid addiction, and offers an interesting avenue for understanding the formation of prescription opioid dependence in clinical populations.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.07/JJ2

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** GR124704

**Title:** Exploring Methylone (TSND-201) as a Rapid-Acting, Non-Hallucinogenic Therapeutic for Opioid Use Disorder

**Authors:** \*E. KONG<sup>1</sup>, J. R. TRINKO<sup>4</sup>, E. FOSCUE<sup>2</sup>, J. WARNER-SCHMIDT<sup>5</sup>, J. TAYLOR<sup>6</sup>, R. J. DILEONE<sup>3</sup>;

<sup>1</sup>Chem., <sup>2</sup>Psychiatry, <sup>3</sup>Dept. Psychiatry, Yale Univ., New Haven, CT; <sup>4</sup>Ribicoff Res. Facilities, Dept. of Psychiatry, Yale Univ. Dept. of Psychiatry, New Haven, CT; <sup>5</sup>Transcend Therapeut., New York, NY; <sup>6</sup>Psychiatry, Yale Univ. Sch. Med., New Haven, CT

**Abstract:** Opioid Use Disorder (OUD) remains a critical public health challenge, particularly among populations where chronic stress exacerbates vulnerability. Current treatments like SSRIs and opioid agonists, are often slow acting, poorly tolerated, or ineffective at preventing relapse. Methylone (TSND-201), a novel entactogen structurally similar to MDMA but lacking hallucinogenic properties, has demonstrated rapid and durable antidepressant-like effects in preclinical studies. This study evaluated the impact of methylone on oxycodone self-administration, withdrawal behavior, and respiratory depression in adult male C57BL/6J mice. Mice were trained to orally self-administer oxycodone under daily 2 hour operant conditioning sessions to establish stable drug-taking behavior on an FR3 schedule. Several doses of methylone were tested in a Latin Square design, each separated by 3 days of drug wash out self-administration sessions, such that every mouse received all doses (0, 5, and 15 mg/kg, ip) 30 min prior to their operant session. No effect on oxycodone self-administration was seen for 5 mg/kg, while a significant increase was found after 15 mg/kg. A separate cohort of mice was trained and tested in an identical manner using progressive ratio (PR) to assess potential effects on motivation to acquire oxycodone and no effect was seen at any dose. To assess effects on precipitated withdrawal symptoms, chronic delivery of oxycodone (130 mg/kg BW/Day) was delivered with subcutaneous osmotic minipumps. On test day, mice were treated with methylone 0, 5, 15, or 30 mg/kg, ip) 30 min prior to naloxone treatment (1.0 mg/kg, ip), and jumping behavior was immediately quantified over 20 min. To test its effects on oxycodone-induced respiratory depression, mice were treated with methylone 30 min prior to increasing doses of oxycodone. We found a significant attenuation of oxycodone-induced respiratory depression after treatment with 15 and 30 mg/kg ( $p < 0.05$ ). Together, these findings suggest that while methylone does not reduce oxycodone consumption or drug-seeking under maintenance or PR conditions, it may offer therapeutic benefit during opioid withdrawal, or overdose, and could be explored further for relapse prevention strategies.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM



**Program #/Poster #:** PSTR239.08/JJ3

**Topic:** H.08. Drugs of Abuse and Addiction

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NIH/NIDA R00 DA048970  
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**Title:** Ntsr1 identifies a glutamatergic subpopulation of mpf to nac projection neurons implicated in opioid relapse

**Authors:** \*C. LEMCHI<sup>1</sup>, M. HALL<sup>2</sup>, J. M. BORLAND<sup>3</sup>, E. MARRON<sup>4</sup>, P. G. MERMELSTEIN<sup>5</sup>, L. M. SLOSKY<sup>4</sup>;

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**Abstract:** Relapse to opioid use following a period of abstinence is a major obstacle to sustained opioid use disorder (OUD) recovery and is associated with an increased risk of overdose death. Cue-induced reinstatement paradigms in rodent models permit interrogating the circuits driving opioid relapse-like behavior. A convergence of human and animal data suggest that glutamatergic projections from the medial prefrontal cortex (mPFC) to the nucleus accumbens core (NAcC) can regulate drug seeking in response to associated cues. Neurotensin receptor 1 (NTSR1) is a Gq-coupled neuropeptide receptor expressed in brain regions associated with reward and drug seeking, including the mPFC and NAcC. NTSR1 can modulate glutamate and its ligands bidirectionally regulate reinstatement behavior in rodents. We recently identified NTSR1-expressing neurons in the mPFC that project to the NAcC. We hypothesize that NTSR1 identifies a subpopulation of glutamatergic mPFC to NAcC projection neurons that preferentially contribute to opioid relapse. To characterize the cellular identity of NTSR1-expressing neurons in the mPFC, we used RNAscope multiplex fluorescent in situ hybridization in adult male and female C57BL/6J mice, finding that the majority of NTSR1-expressing cells (>80%) co-expressed glutamatergic markers vGlut1 or vGlut2. In comparison, only a minority (2%) expressed only the GABAergic marker Gad1. Approximately 17% of NTSR1-expressing cells did not co-label with vGlut1, Glut2, or Gad1. To further our understanding of this cell population, we analyzed spatial transcriptomic data from the Allen Brain Cell Atlas. In the MERFISH dataset, which assigns cell types based on transcriptomic signatures, 98% of NTSR1-expressing cells in a mPFC region of interest, which contained both the prelimbic and infralimbic cortices, were glutamatergic cell classes, predominantly the intratelencephalic and corticothalamic subclasses. 1% of NTSR1-expressing cells in this region were classified as GABAergic and <1% as non-neuronal. Together, these results suggest that NTSR1-expressing cells in the mPFC are predominantly glutamatergic. To assess the proportion of mPFC to NAcC projection neurons that express NTSR1, we are using a retrograde tracing approach. Data to date indicate that NTSR1 may be a marker of excitatory corticostriatal projection neurons in the mPFC, supporting further investigation of this population's functional role in opioid relapse. Identifying circuit-defined molecular targets, such as NTSR1, offers new opportunities to develop more precise therapeutic interventions for OUD.

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**Poster**

**PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.09/JJ4

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** National Institute on Drug Abuse Intramural Research Program

**Title:** Pharmacological Treatment Targeting Three Main Amygdala Populations in Opioid-Related Behaviors

**Authors:** \*F. BURTON<sup>1</sup>, H. OO<sup>1</sup>, L. SILVA TORTORELLI<sup>1</sup>, L. F. VENDRUSCOLO<sup>1,2</sup>;  
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**Abstract:** Opioid use disorder (OUD) is a chronic psychiatric disorder that is driven by opioid's rewarding effects and the alleviation of somatic and motivational withdrawal symptoms. Fentanyl is a potent synthetic opioid that has been linked to most opioid-related deaths in the United States in recent years. Additional pharmacological treatments for OUD are urgently needed. The central nucleus of the amygdala (CeA) coordinates behavioral processes that are impacted by OUD. Among the different neuronal populations within the CeA, we pharmacologically targeted protein kinase C- $\delta$  (PKC $\delta$ ), corticotropin-releasing factor (CRF), and somatostatin (SST), which modulate pain and other drug-related behaviors. Prior work in our laboratory with Cre-expressing mice showed that these three distinct neuronal populations modulated different opioid withdrawal-related behaviors. The chemogenetic inhibition of PKC $\delta$  in the CeA decreased mechanical sensitivity and reduced operant fentanyl vapor self-administration. The inhibition of CRF in the CeA decreased signs of irritability and somatic withdrawal. The activation of SST in the CeA also decreased signs of somatic withdrawal. We tested effects of systemic treatments with the CRF<sub>1</sub> receptor antagonist R121919, SST-4 receptor agonist J-2156, general PKC inhibitor BIM, and specific PKC $\delta$  inhibitor Tat-dv1-1 on opioid intake, signs of somatic withdrawal, mechanical sensitivity, and irritability in male and female mice. The inhibition of PKC $\delta$  with both BIM and Tat-dv1-1 decreased mechanical sensitivity. The activation of SST with J-2156 decreased signs of somatic withdrawal. The inhibition of CRF with R121919 had no behavioral effects. These findings are consistent with our previous chemogenic manipulations in the CeA, showing that the pharmacological inhibition or activation of different cell populations has different effects on opioid withdrawal-related behavior. Further studies are warranted to understand the biological mechanisms by which different neuronal populations control different behaviors and suggest that these drugs could have potential to treat specific symptoms of OUD.

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**Poster**

**PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

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**Topic:** H.08. Drugs of Abuse and Addiction

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DoD W81XWH-21-10742  
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UAB Start-up Package

**Title:** Tiam1-mediated synaptic plasticity in the NAc for opioid addiction

**Authors:** \*Q. WANG, F. QIN, C. YAO, L. LI;  
Univ. of Alabama at Birmingham, Birmingham, AL

**Abstract:** Opioid addiction is mediated not only by the positive reinforcing effects of opioids, but also by continued use to avoid the negative consequences of withdrawal (negative reinforcement). The nucleus accumbens (NAc) is a primary site for orchestrating both processes. D1R-MSNs and D2R-MSNs in the NAc receive afferents arising from several cortical and limbic brain regions, and pathway-specific activation of these fibers elicits distinct behavioral responses. Specifically, canonical glutamatergic inputs from the basolateral amygdala (BLA), the ventral hippocampus (vHip), and the medial prefrontal cortex (mPFC) to D1R-MSNs drive reward, while glutamatergic transmission from the thalamic paraventricular nucleus (PVT) to D2R-MSNs has been linked to aversion processing. Rho GTPase family member Rac1 regulates actin cytoskeleton remodeling and modulates drug-induced structural remodeling of MSNs in the NAc. Tiam1 (TIAM Rac1 Associated GEF 1) is a critical regulator of Rac1 that promotes excitatory synaptogenesis by modulating actin cytoskeletal dynamics during brain development. Genome-wide association studies (GWAS) found that Tiam1 expression within the reward-associated brain regions was significantly associated with the phenotypes for opioid use disorder. Our recent studies have shown that in the adult nervous system, Tiam1 not only regulates synaptic structural plasticity through actin cytoskeleton remodeling but also regulates synaptic functional plasticity by stabilizing synaptic NMDARs. Here, we found that in the NAc shell, Tiam1-coordinated synaptic structural and functional plasticity in D1R-MSNs that receive glutamatergic inputs from the BLA, mPFC, and/or vHip drives opioid rewarding behaviors, and in PVT input-defined D2R-MSNs promotes withdrawal symptoms. Furthermore, systemic NSC23766 administration or intra-NAc Tiam1 ASO infusion reduces opioid-seeking behaviors

in mouse models of morphine CPP and heroin self-administration. Our study is significant because it identifies Tiam1-mediated synaptic plasticity within NAc MSNs as the determinant event in opioid addiction and demonstrate a causal link between this plasticity and opioid reward and withdrawal symptoms in a cell type-, subregion-, and circuit-specific manner, which advances our understanding of the complex mechanisms underlying opioid addiction and may provide a promising novel target for future treatment strategies.

**Disclosures:** **Q. Wang:** A. Employment/Salary (full or part-time): University of Alabama at Birmingham. **F. Qin:** A. Employment/Salary (full or part-time): University of Alabama at Birmingham. **C. yao:** A. Employment/Salary (full or part-time): University of Alabama at Birmingham. **L. Li:** A. Employment/Salary (full or part-time): University of Alabama at Birmingham.

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR239.11/JJ6

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH Grant ZIA-DA000602  
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**Title:** Involvement of dynorphin signaling in fentanyl addiction-like behaviors

**Authors:** \***L. A. WARD**<sup>1</sup>, A. GREGORY FLORES<sup>1</sup>, E. R. CARLSON<sup>1</sup>, E. FRYE<sup>1</sup>, L. HASTINGS<sup>1</sup>, L. F. VENDRUSCOLO<sup>1</sup>, G. F. KOOB<sup>2</sup>, R. C. N. MARCHETTE<sup>1</sup>;  
<sup>1</sup>Natl. Inst. on Drug Abuse, Baltimore, MD; <sup>2</sup>Natl. Inst. on Alcohol Abuse and Alcoholism, NIH, Natl. Inst. on Alcohol Abuse & Alcohol NIAAA, Bethesda, MD

**Abstract:** Opioid misuse and overdose deaths are major public health issues in the United States. Initial drug use is motivated by a desire to experience euphoria, while chronic, compulsive drug use is hypothesized to be motivated by the avoidance of or relief from aversive withdrawal symptoms (e.g., hyperalgesia). We hypothesize that compulsive opioid use and withdrawal symptoms are mediated by the endogenous opioid dynorphin (DYN). To test this hypothesis, we utilized mice with a global deletion of the prodynorphin gene (pDYN KO) and DYN-Cre transgenic mice and chemogenetics to investigate the involvement of DYN in compulsive-like opioid intake and withdrawal-induced hyperalgesia. Male and female wild type (WT, 23) and pDYN KO (13) mice first were assessed for thermal sensitivity in a baseline cold plate test (2° C, 1 min). The mice underwent 6 1-hour sessions to acquire fentanyl vapor self-administration, followed by 9 1-hour (short access, ShA) or 6-hour (long access, LgA) sessions to assess the escalation of fentanyl intake. The cold plate test was repeated to examine withdrawal-induced hyperalgesia. Motivation for fentanyl vapor was assessed using a progressive ratio test (6-hour)

where the response requirement for subsequent drug deliveries increased by 6 throughout the session. There were no differences between WT and pDYN KO mice of either sex during ShA self-administration. LgA male but not female pDYN KO mice demonstrated reduced withdrawal-induced hyperalgesia, escalation of fentanyl intake, and motivation for fentanyl compared to WT mice. Sexually dimorphic differences in DYN regulation of pain and motivation have been reported, but its role in the periaqueductal gray (PAG), a region in the midbrain known to modulate hyperalgesia, is unknown. To investigate this role, male and female DYN-Cre mice received intra-PAG injections of AAV-hSyn-hM4Gi-mCherry or AAV-hSyn-hM4Gq-mCherry. These mice were made opioid-dependent by passive fentanyl administration. Cold plate hyperalgesia testing was completed after saline (24 Gi, 18 Gq) or J60 (24 Gi, 23 Gq) administration 1 day (acute) and 8 days (protracted) after the last fentanyl injection. We found that chemogenetic inhibition of DYN cells in the PAG decreased nociceptive responses in females and protracted withdrawal-induced hyperalgesia in males, whereas chemogenetic stimulation of DYN cells increased acute withdrawal-induced hyperalgesia in both sexes. Overall, these findings highlight the importance of DYN signaling in the PAG in opioid intake, motivation, and withdrawal, and support its potential as a viable target for the treatment of opioid use disorder.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR239.12/JJ7

**Topic:** H.08. Drugs of Abuse and Addiction

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**Title:** Behavioral profiling of sequential opioid-stimulant polysubstance use in a translational rodent model

**Authors:** \*S. SAAVEDRA<sup>1</sup>, A. F. GARCIA<sup>2</sup>, N. NASIROVA<sup>2</sup>, S. M. FERGUSON<sup>2</sup>;  
<sup>2</sup>Psychiatry and Behavioral Sci., <sup>1</sup>Univ. of Washington, Seattle, WA

**Abstract:** Concurrent opioid and stimulant use are increasingly common and partly responsible for the recent escalation in drug overdose deaths, yet it is unclear how the interaction of these compounds within the nervous system impact behaviors related to drug use and addiction. The goal of this study was to compare the drug-taking and drug-seeking patterns that emerge following polysubstance and single substance use in a rodent drug self-administration model. We hypothesized that opioid-stimulant polysubstance use would have synergistic effects on

addiction-related behaviors. Adult Sprague Dawley rats (n=52 males, 41 females) with indwelling jugular catheters were trained to lever press for fentanyl (FENT, 7 days/week; 0.0015 mg/kg/infusion), methamphetamine (METH, 5 days/week; 0.1 mg/kg/infusion) or both (POLY). We utilized a sequential model of polydrug use (i.e. separate use of multiple drugs) modeled after human drug use patterns. After acquisition and 3 weeks of drug self-administration, animals completed either extinction and a cue-induced reinstatement of drug-seeking test, or a behavioral economics thresholding test. POLY rats completed tests for only one drug. Total fentanyl intake was significantly increased in POLY rats compared to FENT rats, but there was no difference in total methamphetamine intake between POLY and METH groups. However, POLY rats exhibited significantly higher drug-seeking behavior during extinction and reinstatement for methamphetamine-associated cues compared to METH rats. No differences were seen in fentanyl-seeking behaviors between POLY and FENT rats. In the behavioral economics test, POLY rats preferred a higher initial dose of fentanyl and exerted more effort to obtain fentanyl than FENT rats. Fentanyl demand elasticity significantly decreased with polysubstance history, while there was a non-significant increase in methamphetamine demand elasticity with polysubstance history. However, demand elasticity was lower for methamphetamine compared to fentanyl in animals with a single drug history. Our findings suggest that a history of polysubstance use increases addiction-related behaviors, but the effects are substance-specific. These results may reflect the recruitment of distinct neural circuits arising from polysubstance use compared to those engaged by each substance alone. Ongoing experiments are using light sheet microscopy to map neurocircuit activation patterns that could underlie these behavioral differences. Understanding the neurobehavioral effects of polysubstance use is essential for the development of targeted, effective treatments for polysubstance addiction.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.13/JJ8

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH grant 1T32TR004385  
NIH grant 1T32TR004376  
1UM1TR004405  
College of Pharmacy

**Title:** Pharmacological effects of xylazine in the context of oral fentanyl self-administration in mice

**Authors:** \*L. D. CAYE<sup>1</sup>, K. F. KITTO<sup>2</sup>, C. PETERSON<sup>3</sup>, G. L. WILCOX<sup>5</sup>, C. A. FAIRBANKS<sup>4</sup>;

<sup>1</sup>Pharmacol., <sup>3</sup>Neurosci., <sup>4</sup>Pharmaceutics, Pharmacology, Neurosci., <sup>2</sup>Univ. of Minnesota, Minneapolis, MN; <sup>5</sup>Dept Neurosci, Pharmacol, Univ. Minnesota Med. Sch., Minneapolis, MN

**Abstract:** Xylazine, an alpha 2 adrenergic agonist, has increasingly been detected as an adulterant in samples of illicitly manufactured fentanyl. Reports suggest users seek out this mixture due to its “sedative, calming effects”, a more intense, immediate and a longer lasting high. The pharmacological effects of xylazine administration in the context of fentanyl self-administration are not well understood. To address this gap, we examined the effects of xylazine on fentanyl self-administration, sedation, tactile hypersensitivity, analgesia, opioid-induced hyperalgesia, and GI transit. Female ICR mice, 25-30 g, had access (12 hr, termed long-access) to oral fentanyl (10 mg/L) self-administration in combination with xylazine or saline pretreatment (10 mg/kg, s.c. daily) and oral fentanyl reinstatement (after cessation of xylazine treatment) to better understand xylazine’s effect on the motivational and rewarding properties of fentanyl. Simultaneously, the effects of repeated xylazine administration in fentanyl-consuming mice were studied in the following assays: open-field activity, intrathecal substance P assay, tactile hypersensitivity (vF assay), warm water tail flick, fecal pellet production, and withdrawal. Our investigation revealed that consistent pretreatment with 10 mg/kg xylazine resulted in tolerance to the sedative and analgesic effects of xylazine. However, these mice did not develop tolerance to the gastrointestinal inhibitory effects of xylazine. Our investigation also revealed that the xylazine pretreated mice showed potentiated lever responding in the first three hours of the long access sessions under FR5 and 10 schedules of reinforcement (ANOVA,  $p < 0.05$ ) during both acquisition of fentanyl maintained responding and reinstatement after a period of abstinence and extinction. Together, these findings suggest that once daily subcutaneous xylazine (10 mg/kg) produces tolerance to sedation and analgesia, but not inhibition of GI transit. Additionally, xylazine pretreatment may potentiate fentanyl maintained responding at higher schedules of reinforcement both during the acquisition period and a period of fentanyl reinstatement.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.14/JJ9

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH T32 DA007237-35

**Title:** Psilocybin reduces heroin seeking in a preclinical model of opioid self-administration through a putative IL-17a mechanism

**Authors:** \*A. D. STRINGER<sup>1</sup>, S. DAWS<sup>2</sup>;

<sup>1</sup>CSAR, Temple Univ. Lewis Katz Sch. of Med., Philadelphia, PA; <sup>2</sup>CSAR, Temple Univ., Philadelphia, PA

**Abstract:** Over half a million people in the USA have died from overdoses involving opioids since the beginning of the opioid crisis in the 1990s. FDA approved treatment options for patients seeking recovery are methadone, buprenorphine and naltrexone, all of which come with burdensome restrictions, the risk of precipitating withdrawal or overdose, and or inadequate control of user craving. Individuals living with opioid use disorder (OUD) need alternatives to pharmacologically treat and support their recovery. Psilocybin is a 5-HT<sub>2A</sub>R agonist with demonstrated therapeutic value for treatment of substance use disorder. Previous preclinical studies from our lab of heroin self-administration (SA) found acute treatment of psilocybin to male rats during forced abstinence results in a reduction of seeking behavior during relapse testing. Administration of a 5-HT<sub>2A</sub>R antagonist in the same model increased craving. We hypothesized these effects to be acute, and using the same model have found no reduction in craving behavior when psilocybin is administered 48 hours prior to relapse testing. Additionally, literature suggests female persons to have increased drug taking. We demonstrated female rats do display significantly increased taking behavior when allowed to administer the same dose of heroin as males. We hypothesized psilocybin pre-treatment on relapse testing to be equally effective in female rats in the same heroin SA model, however; no reduction of seeking behavior was observed. Our prior studies demonstrated IL-17a expression is down-regulated following psilocybin treatment and male rats in a heroin SA model receiving a PFC infusion of IL-17a antibodies during forced abstinence display reduced seeking behavior. Our current study shows rats given IL-17a antibody systemically also display reduced opioid seeking. Overall psilocybin may contribute to a neuronal anti-inflammatory environment that is effective in reducing drug seeking during relapse by impacting IL-17a. This work was supported by NIDA T32 DA007237-35

**Disclosures:** A.D. Stringer: None. S. Daws: None.

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.15/JJ10

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH DA046522 (A-CB)  
CaaMTech Sponsorship

**Title:** The behavioral and cellular effects of psilocin on fentanyl seeking in male and female mice



**Authors:** \*T. N. LOVELL<sup>1</sup>, A.-C. BOBADILLA<sup>2</sup>;  
<sup>2</sup>Biomed. Sci., <sup>1</sup>Colorado State Univ., Fort Collins, CO

**Abstract:** Psychedelic compounds show therapeutic promise for a variety of human health disorders, including substance use disorders. A hallmark of substance use disorder is context-induced relapse, wherein re-exposure to the environmental cues associated with drug use can trigger drug-seeking behavior. Utilizing a Conditioned Place Preference associative learning paradigm, we explored the impact of the psychedelic compound, psilocin, on context-induced fentanyl seeking in male and female wild-type C57BL/6J mice, emphasizing sex as a biological variable. Subjects were conditioned for eight days to pair environmental contexts with fentanyl or saline injections, then administered varying doses of psilocin and evaluated for fentanyl-seeking behavior, measured as the percentage of time spent in the fentanyl-paired context. We show that psilocin reduces fentanyl seeking exclusively in females, with no impact in males. Additionally, when evaluated for anxiolytic and anxiogenic properties in the Elevated Plus Maze behavior model, psilocin elicited no significant changes in anxiety-like behaviors in males or females compared to controls. For a preliminary assessment of the effect of psilocin on fentanyl seeking at the neuronal level, intact tissue clearing, light-sheet microscopy, and 3D mapping were conducted on brain samples collected from transgenic Ai14xcFos-TRAP2 mice, and the activation of psilocin- and fentanyl-linked fluorescence-labeled cell populations was compared across brain regions and sexes. Together, these findings suggest psilocin as an effective therapeutic candidate for fentanyl use, particularly for females. Follow-up experiments will include estrous cycling and hormone profiling of female mice throughout testing to understand the behavioral and cellular roles of reproductive hormones in psilocin-mediated decreases in fentanyl seeking.

**Disclosures:** T.N. Lovell: None. A. Bobadilla: None.

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.16/JJ11

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH Grant UG3DA050942  
NIH Grant UL1TR002544  
Program in Pharmacology and Drug Development, Tufts Univ. Grad Sch  
Biomed Sciences

**Title:** An Intranasal GDNF gene therapy for opioid relapse reduction: Effects on central dopamine exocytosis in oxycodone-seeking rats

**Authors:** Y. R. ABUHASAN<sup>1</sup>, L. LI<sup>1</sup>, J. S. YANG<sup>1</sup>, S. A. AGRAWAL<sup>1</sup>, J. EGHOLM<sup>1</sup>, K. E. BUDGE<sup>2</sup>, O. SESENOGLU-LAIRD<sup>3</sup>, R. C. MOEN<sup>3</sup>, M. J. COOPER<sup>3</sup>, B. L. WASZCZAK<sup>4</sup>, E.

M. BYRNES<sup>2</sup>, \*E. N. POTHOS<sup>1</sup>;

<sup>1</sup>Immunology, Grad. Program in Pharmacol. and Drug Develop., Tufts Univ. Sch. Med., Boston, MA; <sup>2</sup>Tufts Univ. Cummings Sch. of Vet. Med., North Grafton, MA; <sup>3</sup>Copernicus Therapeutics, Inc., Cleveland, OH; <sup>4</sup>Dept Pharmaceut Sci., Northeastern Univ., WELLESLEY HILLS, MA

**Abstract:** The ongoing opioid epidemic has underlined the need for treatment of opioid use disorder (OUD) with alternatives to methadone and buprenorphine. Such interventions should impact in a beneficial manner the central dopamine systems mediating opioid reward and the aversive aspects of opioid withdrawal and abstinence. Our prior work has shown that glial cell derived neurotrophic factor (GDNF) has protective effects on midbrain dopamine neurons and synaptically facilitates dopamine release. We and others have prior evidence that chronic use of opioids and the aversive states of opioid withdrawal and abstinence are associated with chronic defects in mesolimbic dopamine release, which can drive relapse. Our current studies have so far demonstrated that intranasal administration of GDNF plasmid DNA nanoparticles (pGDNF NPs) reduce central dopamine deficits in the medial prefrontal cortex in a rat model of oxycodone (OXY) intravenous self-administration (IVSA) and also reduce drug-seeking behavior by about 20%. In the present work we considered whether changes in dopamine exocytosis in real time correlate with behavioral parameters of OXY IVSA that assess motivation to work for OXY injections. We examined *ex vivo* dopamine release kinetics in dorsal striatum (DS), nucleus accumbens (Nacc), and medial prefrontal cortex (PFC) of rats trained in OXY IVSA, followed by 28 days of abstinence. Recording electrodes with 5  $\mu$ m carbon fibers (Amoco) and a positive 700 mV voltage (vs Ag-AgCl ground) were placed in 300  $\mu$ m coronal sections of the DS, Nacc or PFC. A bipolar stimulating electrode was placed 100-200  $\mu$ m away from the carbon fiber electrode and a current stimulus of +500  $\mu$ A was applied 3 times per site every 5 min for 2 msec in order to electrically evoke dopamine exocytosis. We then ran correlation analyses between behavioral (IVSA) and dopamine release parameters to detect any differences between pGDNF NP and saline-treated groups. We found that there was a positive correlation between fixed-ratio 5 (FR-5) lever pressing for oxycodone before treatment and dopamine exocytosis in PFC after treatment with pGDNF NPs (Spearman's R: 0.5908,  $p < .01$ ). There was also a positive correlation between progressive ratio (PR) responding and dopamine exocytosis in the PFC (Spearman's R: 0.4257,  $p < .05$ ) in pGDNF NP-treated animals. Saline-treated groups did not feature such correlations. These results indicate that intranasal treatment with pGDNF NPs has a greater impact on animals with higher oxycodone-seeking behavior prior to treatment and support our hypothesis that correction of dopamine deficiencies may be a mechanism for the efficacy of the pGDNF NPs in reducing relapse behavior.

**Disclosures:** Y.R. Abuhasan: None. L. Li: None. J.S. Yang: None. S.A. Agrawal: None. J. Egholm: None. K.E. Budge: None. O. Sesenoglu-Laird: A. Employment/Salary (full or part-time): Copernicus Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Copernicus Therapeutics, Inc. R.C. Moen: A. Employment/Salary (full or part-time): Copernicus Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Copernicus Therapeutics, Inc. M.J. Cooper: A. Employment/Salary (full or part-time): Copernicus Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Copernicus Therapeutics, Inc.. B.L. Waszczak: None. E.M. Byrnes: None. E.N. Pothos: None.

## Poster

### PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.17/JJ12

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH/NIDA UG1DA050209 Clinical Laboratories with Integrated Neuroscience (Kampman and Childress MPI)

**Title:** Testing the dopamine D3 receptor partial-agonist in Opioid Use Disorder (OUD)

**Authors:** \*A. CHILDRESS<sup>1</sup>, P. S. REGIER<sup>2</sup>, A. TUFANOGLU<sup>2</sup>, N. HAGER<sup>2</sup>;

<sup>1</sup>Univ. PENN Perelman Sch. of Med., St. Davids, PA; <sup>2</sup>Psychiatry, Univ. PENN Perelman Sch. Med., Philadelphia, PA

**Abstract:** **AIM:** Philadelphia has the third highest rate of opioid overdose deaths in the country, with fentanyl present in 82% of fatal opioid overdoses, and in nearly half of cocaine overdoses. Medication-assisted treatment (MAT) for opioid use disorders (OUD) is critical for reducing illicit use, and for preventing overdose deaths. Unfortunately, MAT compliance is often poor. Finding promising adjunctive medications could save thousands of lives each year. Dopamine D3 partial agonists or antagonists offer promise as anti-relapse medications across a range of abused substances, including opioids, cocaine, nicotine and alcohol. As D3-specific agents for humans are still in development, we have begun testing cariprazine (CRZ), a commercially-available medication with high D3 (vs. D2) affinity, for clinical, brain and behavioral impacts in individuals with Opioid Use Disorder. **METHODS:** We are conducting a phase IIa, randomized, single-blind, placebo-controlled pilot study (8 outpatient weeks; twice weekly urines; n=25, ongoing) of low-dose CRZ (1.5mg/d) vs. placebo (PBO) in OUD outpatients who are already taking a stable dose of either methadone or buprenorphine. A battery of relapse-relevant behavioral and neurocognitive tasks, along with fronto-cortical (fNIRS) and whole brain (fMRI/BOLD) probes for reward, inhibition and decision-making, are collected at designated timepoints (e.g., baseline, steady-state). For the current poster, we conducted an interim analysis of retention, adherence, and drug use outcomes (after steady state) for the CRZ vs. PBO participants (two-tailed t; p<0.05). **RESULTS:** A 2:1 randomization ratio yielded 14 CRZ and 7 PBO participants. Retention/adherence was strong (averaging 81.3%), and did not differ between the groups (p>0.05). Fentanyl-positive urines did not differ (p>0.05) between the groups (44.5 vs 45.2 %, CRZ vs. PBO). Cocaine-positive urines use did not differ (p>0.05) between the groups (41.7 % vs 25%, CRZ vs. PBO). **CONCLUSION:** This preliminary analysis of retention and drug use outcomes for 1.5 mg CRZ in OUD did not detect group differences. However, as clinical outcomes are multi-determined, brain and behavioral tasks are often a more sensitive probe for differential effects of medications; these additional analyses are ongoing. Also worth noting, for this initial study, we tested lowest dose of CRZ as this offered the strongest D3 vs. D2 affinity (and minimized side effects). It is possible, however, that a balance of D3-D2 actions

may be clinically helpful -supporting future testing of the 3 mg dose that demonstrated encouraging differential brain effects in our prior pilot study of CRZ in primary cocaine users.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.18/JJ13

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** 7R21DA060503-02  
5R35GM150513-02  
R21DA060503  
R35GM150513  
R01DA043247  
I01BX006642

**Title:** Identification of neuronal subpopulations most affected in the orbital frontal cortex of heroin users

**Authors:** \*F. CHANG<sup>1,2</sup>, A. KOZLENKOV<sup>3,4</sup>, G. ROMPALA<sup>5</sup>, J. JUNG<sup>5,4</sup>, Y. L. HURD<sup>5</sup>, Z. DUREN<sup>1</sup>, S. DRACHEVA<sup>5,4</sup>;

<sup>1</sup>Indiana Univ. Sch. of Med., Indianapolis, IN; <sup>2</sup>Clemson Univ., Clemson, SC; <sup>3</sup>Friedman Brain Inst. and Dept. of Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY; <sup>4</sup>James J. Peters VA Med. Ctr. and VISN 2 MIRECC, Bronx, NY; <sup>5</sup>Friedman Brain Inst. and Dept. of Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

**Abstract:** Opioid use disorder (OUD) is a major public health crisis in the United States, with approximately 70,000 opioid-related overdose deaths reported in 2022 and societal costs exceeding \$1 trillion. Opioids such as morphine and heroin are known to induce transcriptional and epigenetic changes in both rodent and human brains. However, most OUD studies have focused on bulk tissue, overlooking the cellular diversity of the brain, where each cell type possesses a unique transcriptional and epigenetic landscape. We hypothesize that specific neuronal and glial subpopulations are particularly susceptible to the effects of chronic opioid exposure. To investigate this, we conducted single-nucleus (sn) multiome analysis using 10x Genomics technology to simultaneously profile gene expression (snRNA-seq) and chromatin accessibility (snATAC-seq) within the same nuclei. 331 thousands nuclei were isolated from postmortem human orbitofrontal cortex (OFC)—a brain region repeatedly implicated in OUD—obtained from 14 heroin users and 12 matched controls. We performed differential analysis to identify differentially expressed genes (DEGs) and differentially accessible regions (DARs), and found that each cell type had, on average, hundreds of DEGs and thousands of DARs. Enrichment analyses were then performed using multiple strategies: -Gene Set Enrichment

Analysis (GSEA) revealed significant enrichment of morphine addiction-related gene sets (KEGG) in Layer 6 intratelencephalic (L6 IT), L6 IT Car3, and L6b neuronal subtypes. MAGMA analysis using OUD GWAS data and cell type-specific DEGs identified significant enrichment of downregulated genes in L6 IT, L6 IT Car3, and Pvalb interneurons. Gene regulatory network analysis using LINGER identified two modules enriched for DEGs across multiple cell types, one of which was significantly associated with the morphine addiction gene set. Notably, this module showed strong enrichment for DEGs derived from L6 IT and L6 IT Car3 neurons, reinforcing results from both the GSEA and MAGMA analyses. Interestingly, L6 IT Car3 cells also exhibited specific enrichment for kappa opioid receptors (OPRK1)—a key component of the dynorphin/OPRK1 system, which has been implicated in dysphoria and the “anti-reward” state associated with opioid withdrawal. Together, these findings highlight deep-layer intratelencephalic neurons as selectively vulnerable to transcriptional and epigenetic dysregulation in OUD. They also point to distinct molecular pathways that could serve as targets for future therapeutic strategies aimed at mitigating the long-term effects of opioid addiction.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.19/JJ14

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH DA K01

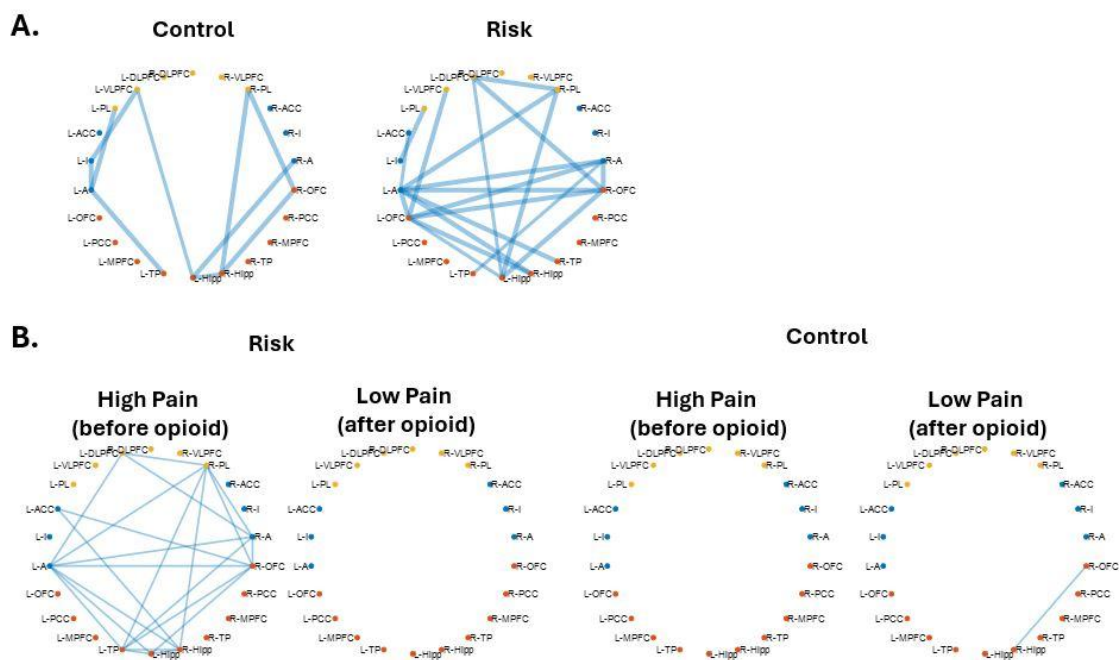
**Title:** Altered limbic connectivity in patients vulnerable to opioid use disorder

**Authors:** \*J. RYU<sup>1</sup>, M. TOLOSSA<sup>1</sup>, A. BARI<sup>2</sup>;

<sup>2</sup>Neurosurg., <sup>1</sup>UCLA, Los Angeles, CA

**Abstract:** Substance use disorder (SUD), chronic pain, and depression are risk factors for developing opioid use disorder (OUD). These conditions have been linked to heightened pain processing; however, the underlying neural mechanisms that shape how individuals experience pain and how opioid use alters neural connectivity remain poorly understood. This study aims to clarify how altered neural connectivity contributes to pain perception and opioid risk in this population. We recorded local field potentials (LFPs) from 33 epilepsy patients with intracranial depth electrodes implanted for seizure monitoring (200 Hz). Targeted regions included the amygdala (N=21), hippocampus (N=31), dorsolateral prefrontal cortex (N=12), anterior cingulate cortex (N=12), orbitofrontal cortex (N=20), insula (N=9), medial prefrontal cortex (N=1), and ventrolateral prefrontal cortex (N=17). LFPs were extracted 15 minutes before and after opioid or acetaminophen administration and filtered in the theta/alpha band (4-15 Hz). Signals were compared between patients

with OUD risk factors (risk group; N=23) and those without (control group; N=10). Connectivity was assessed using cross-correlation of enveloped time series across these regions, with statistical significance determined via permutation tests with Bonferroni correction. Pain medications were administered more frequently to the risk group, suggesting altered pain processing in these individuals. During pain epochs, the risk group's limbic connectivity was denser than controls (Fig A). Following opioid administration during pain episodes, connectivity further decreased in the risk group, whereas it remained stable in controls (Fig B). Acetaminophen had no significant effect on connectivity in either group. These findings suggest that individuals at risk for OUD exhibit differences in limbic connectivity. The further reduction in connectivity following opioid use highlights its distinct impact on the limbic system and may inform development of targeted neuromodulatory treatments for OUD and its underlying risk factors.



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**Poster**

**PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.20/JJ15

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NSERC RGPIN-2023-04731  
CIHR PJT-186231

**Title:** The role of the anterior paraventricular nucleus of the thalamus in cue-induced heroin seeking in abstinent male and female rats

**Authors:** \*E. G. AH-YEN<sup>1</sup>, C. BORGES<sup>1</sup>, U. SHALEV<sup>2</sup>;  
<sup>2</sup>Dept. of Psychology, <sup>1</sup>Concordia Univ., Montreal, QC, Canada

**Abstract:** Drug addiction is a chronic disorder characterized by a cycle of excessive drug use, abstinence, and relapse. Relapse poses a substantial obstacle to addiction treatment, and the risk for relapse is exacerbated by chronic food restriction. However, the underlying neuronal mechanisms are unknown. The paraventricular nucleus of the thalamus (PVT) has been shown to have an important role in drug seeking. The PVT can be anatomically and functionally divided into the anterior (a) PVT and posterior (p)PVT. Our laboratory has demonstrated a role for the pPVT in food restriction-induced augmentation of heroin seeking in abstinent rats. Here, we chemogenetically and pharmacologically inhibited the aPVT in male and female rats to examine cue-induced heroin seeking. We then chemogenetically activated the aPVT to further understand its role in cue-induced heroin seeking. Rats were trained to self-administer heroin (0.1mg/kg/infusion) for 10 days, followed by 16 days of forced abstinence. During forced abstinence, rats were either sated or food restricted. On day 15 of food restriction, rats either received a vehicle or had their aPVT inactivated or activated and underwent a heroin-seeking test under extinction conditions. In both experiments, we found that food-restricted rats pressed more for heroin than their sated counterparts. Chemogenetic and pharmacological inhibition of the aPVT had no significant effect on cue-induced heroin seeking in male rats. However, chemogenetic inhibition of the aPVT in female rats increased cue-induced heroin seeking. Chemogenetic activation of the aPVT decreased cue-induced heroin seeking in male rats, but had no significant effects on cue-induced heroin seeking in female rats. These findings suggest that the aPVT and pPVT may not be functionally distinct under our conditions and that the aPVT may play an inhibitory role in cue-induced heroin seeking under these conditions.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.21/JJ16

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIDA grant R01 DA055849

**Title:** Ventral Pallidum GABA Neuron Regulation of Brain-Wide Neural Networks Underlying Opioid Relapse

**Authors:** \***B. MORALES**<sup>1</sup>, H. RAMIREZ<sup>2</sup>, C. RUIZ<sup>3</sup>, Y. XIE<sup>2</sup>, S. V. MAHLER<sup>2</sup>;

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**Abstract:** The ventral pallidum (VP) is a key node in the neural networks underlying motivated behaviors, including the reward and stress networks involved in relapse in opioid addiction. We previously showed in rats that VP GABA neurons are required for cues and contexts to reinstate opioid seeking after voluntary (punishment-induced) abstinence. Here, we investigate the wider neural networks activated during reinstatement of drug seeking, and compare them to the activity seen in a context in which drug seeking was suppressed by the threat of negative consequences. Furthermore, we examine how acutely inhibiting VP GABA neurons in either context, and in both sexes, alters the structure of these relapse-relevant, brain-wide neural networks. Rats were first trained in a “Safe Context” (Context A) to self-administer the rewarding opioid drug remifentanyl and a tone/light cue by pressing a lever. They were then moved to a “Dangerous” Context B, where lever presses still yielded remifentanyl and a cue but also a foot shock punishment on 50% of trials, which eventually caused all rats to voluntarily suppress their drug seeking. On the final test day, rats were returned to either Context A or B, where they received cues upon lever pressing, but no further drug or shock. We targeted inhibitory DREADDs (or mCherry only) to VP GABA neurons in male and female GAD1:Cre rats, allowing on-demand inhibition of these cells during behavior by injecting CNO (5mg/kg). As expected, inhibiting VP GABA neurons suppressed relapse-like drug seeking in Context A, without consistently affecting seeking in Context B. Rats were perfused after the last session, and brains were processed for c-Fos IHC, and co-expression of cell type markers in some cases. We analyzed c-Fos expression density in 35 cortical, striatal, pallidal, thalamic, mid-, and hindbrain. We found that Contexts A and B differentially elicited activity in these networks, relative to each other, and to home-cage control groups. Furthermore, inhibiting VP GABA neurons robustly altered activity patterns in wider neural networks, and did so in a sex- and context-dependent manner. Results point to a key role for VP GABA neurons within addiction- and relapse-related brain networks and may thus inform future treatment strategies in humans struggling not to relapse to opioid drug use.

**Disclosures:** **B. Morales:** None. **H. Ramirez:** None. **C. Ruiz:** None. **Y. Xie:** None. **S.V. Mahler:** None.

**Poster**

**PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.22/JJ17

**Topic:** H.08. Drugs of Abuse and Addiction

**Title:** Investigating nucleus accumbens circuits underlying associative learning and prescription opioid seeking in mice



**Authors:** \*E. BARRERA<sup>1</sup>, S. J. HERRERA<sup>2</sup>, L. ALTHAWADI<sup>2</sup>, J. A. BEELER<sup>2,1</sup>;  
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**Abstract:** Opioid addiction is a major public health issue often resulting in relapse. Environmental stimuli obtain the capacity to initiate drug-seeking through synaptic adaptations underlying drug-reinforcement. How these systems adapt across drug- and reward- learning in the indirect and direct pathway of the nucleus accumbens core (Nacc) is not fully understood. We have 1. developed a model of oxycodone oral self-administration using C57BL6 mice (N = 32, n = 4 per reinforcer solution, half of each sex) and 2. implemented in-vivo multiplex fiber photometry across Pavlovian conditioning targeting D2 medium spiny neurons (iMSNs) using A2A-cre mice (3 males, 2 females), cre-dependent glutamate (iGluSnFR3) and calcium (jRCaMP1a) fluorescent sensors. In experiment 1. Mice were trained to self-administer (SA) water after post-prandial thirst on an FR1 schedule of reinforcement. Following water SA mice were randomly assigned to self-administer water, citric acid (CA, .02 mg/ml) or oxycodone (.2, .5, .8, 2, 4, 7mg/ml) without post-prandial thirst (NPP). After 15 days of NPP SA, mice underwent 15 days of extinction, followed by a cue-induced reinstatement test. Following reinstatement, all mice underwent 10 days of SA and tested for 5 days in a PR2 task. Finally, mice were tested for naloxone (3mg/kg) precipitated withdrawal. We found that lever pressing for water and oxycodone across 15 days of NPP SA was significantly greater than that of CA which showed to be comparable in aversiveness to that of oxycodone (.2 - .8 mg/ml). Further, we found that mice that self-administered 2mg/ml oxycodone reinstated significantly more than the CA controls. Lever pressing and breakpoints in the .8 and 2mg/ml oxycodone groups were significantly greater than CA controls under a PR2 schedule of reinforcement, these breakpoints were positively correlated with total jumps in our naloxone experiment, however .2mg/ml oxycodone was not sufficient for the induction of naloxone precipitated withdrawal. In experiment 2, we found that the acquisition of a light conditioned stimulus (CS) paired with the delivery of 50% condensed milk (US) after 6 days of CS-US pairing was associated with the increase of glutamate neurotransmission and simultaneous increase of iMSN activity. These data suggest that glutamate inputs to iMSNs may acquire CS representations driving iMSN activity. Together, these data provide an avenue for assessing pre- and post- synaptic adaptations in-vivo in a circuit specific manner in a model of prescription opioid addiction and may aid in the development and understanding of treatment strategies aimed at reducing relapse.

**Disclosures:** E. Barrera: None. S.J. Herrera: None. L. Althawadi: None. J.A. Beeler: None.

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.23/JJ18

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:**

W.M. Keck Foundation Research Program Phase II  
U01DA043799  
K00DA057923

**Title:** Addiction index predicts withdrawal-induced allodynia following intravenous oxycodone self-administration in heterogenous stock rats

**Authors:** \*S. L. PLASIL<sup>1,2</sup>, L. TIEU<sup>2</sup>, J. QIAN<sup>2</sup>, N. TAYLOR<sup>2</sup>, E. A. SNEDDON<sup>2</sup>, S. BONNET-ZAHEDI<sup>2</sup>, L. L. CARRETTE<sup>2</sup>, M. BRENNAN<sup>2</sup>, B. SICHEL<sup>2</sup>, D. OTHMAN<sup>2</sup>, A. MORGAN<sup>2</sup>, M. KALLUPI<sup>2</sup>, G. DE GUGLIELMO<sup>2</sup>, O. GEORGE<sup>2</sup>;

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**Abstract:** Pain contributes to opioid misuse, withdrawal, and relapse. In humans, opioid withdrawal is associated with allodynia, however, in preclinical settings, the relationship between opioid-induced allodynia and addiction-like behavior severity remains unclear. We hypothesize that oxycodone intravenous self-administration and withdrawal-induced allodynia are correlated, and this relationship is strengthened or weakened by the individual's Addiction Index. Genetically diverse male and female heterogeneous stock rats underwent oxycodone self-administration [short (2 hours/session, 4 sessions) and long (12 hours/session, 14 sessions) access]. Progressive ratio responding, tail immersion, and Von Frey tests were performed throughout. Addiction Indices for oxycodone were derived from the Z-scores of intake escalation, motivation to consume, mechanical sensitivity during withdrawal, and analgesic tolerance. Allodynia was assessed at six timepoints throughout withdrawal (4 hours, 12 hours, 1 day, 1 week, 2 weeks, and 3 weeks). Linear regression and correlation matrices examined associations between allodynia and self-administration metrics, including fixed and progressive ratio responding, and short and long access to intravenous oxycodone. Oxycodone self-administration induced significant allodynia at 12 hours, 1 day, and 2 weeks into withdrawal, with recovery by week 3. Rats were stratified by Addiction Index using a median split. Both High and Low Addiction Index groups showed significant allodynia at 12 hours and 1 day. Low Addiction Index began to recover at 1 day and returned to baseline by 1-week, while High Addiction Index exhibited sustained hypersensitivity throughout testing. In the High Addiction Index group, allodynia at 1 day and 2 weeks negatively correlated with late-phase oxycodone intake. No significant correlation was observed for Low Addiction Index. No sex differences were observed. Withdrawal from oxycodone induces protracted allodynia, with severity and length stratified by individual addiction-like behaviors. The High Addiction Index group displayed heightened and prolonged allodynia compared to Low Addiction Index, suggesting that withdrawal-induced allodynia may contribute to the higher relapse rates of drug seeking observed in High Addiction Index during self-administration. Correlation analysis and matrices highlight oxycodone self-administration metrics as potential predictors for subsequent withdrawal-induced allodynia. These findings suggest mechanical sensitivity during withdrawal may reflect individual differences in addiction vulnerability.

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**Poster**

## **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.24/JJ19

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH grant UH3 DA050325

**Title:** Acute glucagon-like peptide-1 receptor agonist, semaglutide, attenuates cue-, drug-, and stress-induced fentanyl seeking in male sprague dawley rats

**Authors:** \*C. BRANDL<sup>1</sup>, B. EVANS<sup>3</sup>, E. SHEALY<sup>4</sup>, J. E. NYLAND<sup>2</sup>, P. S. GRIGSON<sup>2</sup>;  
<sup>2</sup>Neural and Behavioral Sci., <sup>1</sup>Penn State Col. of Med., Hershey, PA; <sup>3</sup>Neural and Behavioral Sci., Penn State Col. of Med. Neurosci. Grad. Program, Hershey, PA; <sup>4</sup>Pennsylvania State Univ., Hummelstown, PA

**Abstract:** **Acute Glucagon-Like Peptide-1 Receptor Agonist, Semaglutide, attenuates cue-, drug-, and stress-induced fentanyl seeking in male Sprague Dawley rats** Authors: Chris Brandl<sup>1</sup> & Brianna Evans<sup>1</sup>, Nikhil Acharya<sup>1</sup>, Elise Shealy<sup>1</sup>, Jen Nyland<sup>1</sup>, Chris Freet<sup>2</sup>, Scott Bunce<sup>2</sup>, Patricia Sue Grigson<sup>1</sup>

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Opioid overdose remains a significant public health crisis in the United States, with synthetic opioids like fentanyl contributing to over 48,422 deaths in 2024. Despite the availability of three medications for opioid use disorder (MOUDs)—methadone, buprenorphine, and naltrexone—relapse and overdose rates remain high due to stigma and poor access. Glucagon-like peptide-1 receptor (GLP-1R) agonists, originally developed for Type 2 diabetes and obesity, are gaining attention for their potential to treat substance use disorders. While short-acting GLP-1R agonists like exenatide and liraglutide have shown promise in reducing opioid intake and relapse-like behavior in preclinical models, longer-acting agents like semaglutide may offer better adherence due to less frequent dosing. However, its efficacy in treating opioid use disorder (OUD) remains underexplored. In this study, we investigated whether acute semaglutide treatment can reduce cue-, drug-, and stress-induced fentanyl seeking in adult male Sprague Dawley rats. Following 14 days of fentanyl self-administration (1.85 µg/kg/infusion, 6 h/day), rats were divided into high or low drug-taking groups based on the median splits and received a single subcutaneous injection of semaglutide (0.026, 0.056, or 0.078 mg/kg) or saline (n≈8/cell). Cue-induced seeking, drug-induced reinstatement (non-contingent fentanyl infusion), and stress-induced reinstatement (0.5 mg/kg yohimbine, i.p.) of fentanyl seeking were measured. Statistical analyses included repeated-measures ANOVAs and Tukey post hoc tests. Semaglutide significantly reduced fentanyl seeking across all three relapse modalities and in high and low drug takers. Drug- and stress-induced reinstatement of fentanyl seeking were virtually abolished at all doses,

while cue-induced seeking was dose-dependently attenuated, with the 0.056 and 0.078 mg/kg doses being most effective. Semaglutide also reduced goal-directed behavior as indexed by active vs. inactive spout responding. These findings suggest that semaglutide, a long-acting GLP-1R agonist, has high potential as a novel, non-opioid pharmacotherapy for OUD. This work was supported by NIH grant UH3 DA050325.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.25/JJ20

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH Grant DA044451

**Title:** Sex and oxycodone vulnerability distinctly promote behavioral changes in heterogeneous stock rats

**Authors:** \*S. FOROUTANI<sup>1</sup>, E. A. SNEDDON<sup>3</sup>, J. MOSQUERA<sup>2</sup>, M. BRENNAN<sup>5</sup>, L. L. CARRETTE<sup>4</sup>, M. KALLUPI<sup>6</sup>, O. GEORGE<sup>7</sup>;

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**Abstract:** Opioid use disorder is a persistent public health crisis, driven in part by increasing rates of overdose and limited individualized treatment options. Preclinical studies have identified sex differences in oxycodone sensitivity, yet the relationship between sex and individual vulnerability to addiction-like behavior remains unclear. This study addresses that gap by examining how sex and vulnerability interact to influence behavioral responses to oxycodone. Multiple cohorts of outbred heterogeneous stock rats (N = 740) were used to evaluate oxycodone-related behaviors across four addiction-relevant domains: escalation of intake, motivation to seek oxycodone, withdrawal-induced hyperalgesia, and tolerance to oxycodone-induced analgesia. Rats underwent intravenous self-administration, and estrous cycle phases were monitored by vaginal cytology. Rats were classified into Resilient, Mild, Moderate, or Severe addiction vulnerability groups based on z-scored performance across the four behavioral domains. Greater vulnerability was associated with increased escalation of oxycodone intake and enhanced withdrawal-induced hyperalgesia. Both sexes in the Moderate and Severe vulnerability groups exhibited higher intake and lower mechanical thresholds compared to the Resilient and Mild groups. Motivation to seek oxycodone did not differ between vulnerability groups within

sex but was significantly higher in females than males across all groups. Tolerance to oxycodone-induced analgesia did not vary by vulnerability group or sex; however, males in the Mild group showed greater analgesia than females prior to self-administration. Additionally, females in the Resilient group consumed more oxycodone than males during the final sessions. Estrous cycle phase had no significant effect on any behavioral outcome. These findings underscore the importance of incorporating both sex and behavioral vulnerability classifications into preclinical models. Identifying sex-specific and vulnerability-linked phenotypes may help uncover mechanisms underlying opioid addiction and guide the development of individualized treatment strategies.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.26/JJ21

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH Grant P20GM113109

**Title:** The effects of altering  $\mu$ -opioid receptor functioning within the nucleus accumbens shell in differentially reared rats

**Authors:** \***B. E. WAYMIRE**<sup>1</sup>, D. A. LAUX<sup>2</sup>, M. AZUMA<sup>2</sup>, T. POLTON<sup>3</sup>, M. CAIN<sup>4</sup>;  
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**Abstract:** It is a well-established finding that differential rearing alters both the hedonic responding (liking) and incentive motivation (wanting) for a reward. Compared to isolated rats, enriched rats exhibit decreased wanting yet increased liking for non-drug rewards. The mu ( $\mu$ )-opioid receptor (MOR), particularly within the nucleus accumbens shell (NAcS), is a key modulator of the hedonic value of rewards and plays a central role in motivation and reward-related behaviors. Previous studies in standard-housed (SC) rats indicate that administration of MOR agonist into the NAcS enhances the hedonic value of sucrose. However, there is a gap in pre-existing literature examining the effects of MOR functioning and hedonic value in

differentially reared rats. In the present study we aimed to address this gap by differentially rearing male and female Long Evans (N = 27) rats in three different rearing environments; standard (SC; n = 12) isolated (IC; n = 7) and enriched (EC; n = 8) from postnatal day (PND) 21-51. After rearing, rats were surgically implanted with an intraoral fistula for taste reactivity (TR), and bilateral cannula into the NAcS for MOR agonist manipulation. Using a within-subject design, rats were microinjected with 3 different concentrations of the MOR agonist DAMGO (control (PBS), low (0.01ug), and high (0.1ug)), in the NAcS to measure its effect on the hedonic value of two different sucrose concentrations (low (0.1M), high (0.5M)). Using a repeated-measures ANOVA, our results suggest that administration of DAMGO, regardless of dose, increased hedonic responding in EC rats for both sucrose concentrations when compared to the control group. However, this effect was not seen in IC or SC rats. These findings suggest that differential rearing may altered MOR function within the NAcS, potentially explaining why individuals exposed to adverse early-life environments exhibit less sensitivity to pleasure and increased vulnerability to substance use disorders.

**Disclosures:** B.E. Waymire: None. D.A. Laux: None. M. Azuma: None. T. Polton: None. M. Cain: None.

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.27/JJ22

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIDA Grant U01DA045300  
NIDA Grant K99DA057390

**Title:** Non-neuronal markers of synaptic plasticity associated with heroin vulnerability versus resiliency

**Authors:** \*A. BERCKMUELLER<sup>1</sup>, S. WALTERHOUSE<sup>2</sup>, B. N. KUHN<sup>3</sup>;  
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**Abstract:** The worldwide rise in opioid use disorder (OUD) makes it imperative to elucidate the neurobiological mechanisms contributing to both vulnerable and resilient behavioral phenotypes. Using a preclinical rat model capturing the complex and multidimensional nature underlying individual variation to OUD akin to what is observed in the human population, we have shown distinct behavioral, gross neurobiological and genetic markers associated with vulnerability and resiliency. However, neuroplastic measures, particularly those that are non-neuronal, have yet to be assessed for individual variation in OUD propensity. To that end, markers of neuroplasticity in the prelimbic cortex (PrL), nucleus accumbens core (NAcc) and ventral pallidum (VP), a series circuit necessary for drug relapse behavior, were examined. Following behavioral training

and phenotypic characterization, rats underwent an additional test for heroin cued reinstatement (15-min or 120-min) or extinction training and were sacrificed. Perineuronal nets (PNN), an extracellular matrix component whose degradation is associated with experience-dependent learning, remained at basal density levels in the PrL of vulnerable rats, but were elevated in resilient rats. This augmentation was maintained in the VP for resilient animals, however a marked degradation in VP PNN density was observed for vulnerable rats. No PNNs exist in the NAc of rats. Microglia, the resident immune cells of the brain, have also been associated with opening neuroplastic windows when in a highly ramified (i.e., reactive) structural state. Microglial structural morphology was not altered in the PrL of resilient rats but was shifted toward reactivity in vulnerable animals. Increased microglia reactivity was maintained in the VP of vulnerable rats; however, resilient rats exhibited a shift toward an increase in homeostatic state. Microglia structural morphology in the NAcc is currently underway. Additionally, analysis of PNN and microglial structural plasticity in two additional components of the drug reward circuitry, the lateral hypothalamus and amygdala, are underway. Together, these data highlight the diversity of non-neuronal neuroplastic adaptations that OUD vulnerability, but possibly more importantly OUD resiliency.

**Disclosures:** A. Berckmueller: None. S. Walterhouse: None. B.N. Kuhn: None.

## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.28/KK1

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH Grant 5SC3GM130430-04  
NIH Grant R16GM153699-01

**Title:** Environmental enrichment decreases c-Fos expression in the ventral tegmental area of cue-induced heroin seeking rats

**Authors:** \*A. MANGAL<sup>1</sup>, Z. NACHSHON<sup>1</sup>, N. PATEL<sup>1</sup>, N. SANDOVAL<sup>1</sup>, A. CHIRIBOGA-ZUNIGA<sup>1</sup>, A. AMINOV<sup>1</sup>, R. NISANOV<sup>1</sup>, E. J. GALAJ<sup>2</sup>, R. RANALDI<sup>1,3</sup>;  
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**Abstract:** It is well recognized that opioid addiction is a global health crisis. Many treatment programs and techniques focus on pharmacological treatments that can be paired with behavioral intervention, including cue-exposure therapy. Unfortunately, these forms of treatment have been found to only be useful during the time in which the individual is receiving treatment. After treatment, there is a non-negligible chance that the user will resume substance use, or relapse. We have found that environmental enrichment (EE), a potential treatment that is not contingent on drug taking, is effective in reducing relapse. This study was aimed at testing the hypothesis

that EE is a potential effective treatment for relapse by blunting the ability of drug cues to activate dopamine (DA) neurons in the ventral tegmental area (VTA). A cue-induced reinstatement model was used to study drug seeking in rats that were trained to self-administer heroin. Using RNAscope in situ hybridization, we analyzed DA neuronal activation in the VTA with c-Fos after a cue-induced reinstatement of heroin seeking in EE rats and compared the same to non-EE (control) rats. We found that EE rats showed significantly less cue-induced reinstatement and significantly less c-Fos in DA neurons of the VTA than non-EE rats. These findings suggest that environmental enrichment is blunting the effect of drug-associated cues to activate DA neurons in the VTA.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.29/KK2

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH Grant R16GM153699-01

**Title:** Environmental enrichment reduces drug and drug cue reward in rats self-administering heroin

**Authors:** \*E. CORSO<sup>1,2</sup>, Z. NACHSHON<sup>2</sup>, E. VAYSMAN<sup>2</sup>, A. CHIRIBOGA-ZUNIGA<sup>2</sup>, R. RANALDI<sup>1,2</sup>;

<sup>1</sup>The Grad. Ctr. of the City Univ. of New York, New York, NY; <sup>2</sup>Psychology, Queens Col. of the City Univ. of New York, Flushing, NY

**Abstract:** Opioid use disorder continues to be an issue despite multiple treatment options that are available. Current treatments for those who suffer from opioid use disorder, such as pharmacological treatment and behavioral interventions, can reduce substance use in the short term but fail to provide long-term protection against relapse. Previous studies have shown that environmental enrichment (EE) may be a viable treatment option for relapse due to its capacity to significantly reduce cue-induced reinstatement and facilitate abstinence. One of the possible reasons EE is effective against drug-seeking is that it may affect drug and drug cue reward value. The current study investigated this possibility. We hypothesized that EE reduces reward values. Reward values were studied using an intravenous self-administration model under a progressive ratio schedule of reinforcement. Rats were trained to self-administer heroin and breakpoints for heroin and heroin cue were recorded before and after housing assignment. We found that, for males, breakpoints after housing assignment were significantly lower in EE groups compared to non-EE groups. Drug cue breakpoints followed a similar trend as drug breakpoint but were not



significantly different. We observed no difference in breakpoints between EE and non-EE females. We conclude that a possible mechanism through which EE reduces drug seeking is by reducing drug and drug cue reward values.

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## **Poster**

### **PSTR239: Opioids: Reinforcement, Seeking, and Reinstatement**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR239.30/KK3

**Topic:** H.08. Drugs of Abuse and Addiction

**Support:** NIH NIDA R00DA052624

**Title:** Nucleus accumbens parvalbumin interneurons encode fentanyl cues in intravenous self administration.

**Authors:** \*S. RAGOONADEN<sup>1</sup>, J. TLASECA-AVILA<sup>1,2</sup>, K. M. JOHNSON<sup>1</sup>, E. LEFEVRE<sup>1</sup>; <sup>1</sup>Biomed. Sci., Univ. of Minnesota Med. Sch., Duluth, MN; <sup>2</sup>Col. of St. Scholastica, Duluth, MN

**Abstract:** Introduction. The ongoing opioid crisis, driven in large part by the widespread availability and potency of synthetic opioids like fentanyl, has underscored the urgent need to better understand the neural mechanisms underlying opioid addiction and relapse. The nucleus accumbens (NAc), a central reward hub, plays a crucial role in mediating drug-seeking behavior. Within the NAc, parvalbumin (PV) interneurons, despite comprising only 1-2% of the neuronal population, exert powerful feedforward inhibition over medium spiny neurons (MSNs) and are well positioned to shape local circuit dynamics during reward-related behaviors. Using in vivo fiber photometry, we tested the hypothesis that PV interneurons in the NAc are dynamically engaged in response to fentanyl-evoked drug cues during intravenous fentanyl self administration (IVSA). Methods. PV-2A-Cre male and female mice were stereotactically injected with Cre-dependent calcium biosensor GCaMP, as a marker of neural activity, and implanted with a fiber optic cannula. Subsequently, mice were implanted with indwelling jugular catheters for IVSA. Fiber photometry recordings were conducted throughout a multi-stage IVSA paradigm with 10 days of intermittent access (alternating periods of drug availability and drug unavailability), progressive ratio, 8 days of extinction and cue-induced reinstatement. Results. Under drug-available conditions in the intermittent access paradigm, PV activity significantly increased in response to active, but not inactive lever presses ( $p < 0.01$ ). Houselight presentation, which cued drug unavailable sessions, was found to lead to a robust increase in PV activity ( $p < 0.001$ ). Conversely, houselight extinction which cued drug availability did not elicit a response in PVs. In the assessment for motivation, where lever presses required for drug reward progressively increase, we found that PV activity was augmented in response to rewarded lever presses ( $p < 0.001$ ). In the reinstatement phase, initial cue presentation and reinstated lever

presses elicited an increase in PV activity. Conclusion. These findings reveal that NAc PV interneurons demonstrate distinct activity patterns across key phases of opioid self-administration. Elevated PV activity in response to fentanyl-predictive cues, and fentanyl unavailability suggests that these interneurons play a dynamic role in drug-seeking behavior and reinstatement. Future studies will use dual-color photometry to investigate how these PV responses to drug cues subsequently modulates MSN activity in the NAc microcircuit.

**Disclosures:** S. Ragoonaden: None. J. Tlaseca-Avila: None. K.M. Johnson: None. E. Lefevre: None.

## **Poster**

### **PSTR240: Imaging Human Attention**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR240.01/KK4

**Topic:** I.01. Attention

**Title:** Measuring Neurotransmitter Fluctuations in the Awake, Conscious Human Brain as Modulation of Cognitive Fatigue

**Authors:** \*J. WONG<sup>1</sup>, S. R. BATTEN<sup>2</sup>, T. M. LOHRENZ<sup>3</sup>, J. P. WHITE<sup>4</sup>, L. BARBOSA<sup>3</sup>, V. JATLA<sup>5</sup>, R. W. BINA<sup>6</sup>, S. M. MCCLURE<sup>7</sup>, P. MONTAGUE<sup>8</sup>;

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**Abstract:** Fluctuations in monoaminergic neurotransmitters and their associated neurotransmitter systems regulate arousal, attention, and executive control, making them central to the human brain's response to sustained cognitive load. This key function is particularly relevant in individuals with disrupted sleep-wake cycles as well as in operational settings requiring continuous vigilance, such as in aviation, medicine, and military. Understanding the precise temporal dynamics of dopamine (DA), serotonin (SE), and norepinephrine (NE) in cognitive fatigue remains a key challenge for neuroscience research. Here, we use machine learning coupled with voltametric methods to measure real-time, sub-second measurement of these neurotransmitters from the awake, conscious human brain while participants engaged in a psychomotor vigilance task (PVT) designed to cause cognitive fatigue. Voltammetric measurements were recorded from clinically relevant brain regions of patients undergoing intracranial electrode monitoring in the epilepsy monitoring unit and machine learning methods were used to infer neurotransmitter fluctuations. Individuals completed 100 trials of PVT over a 15-20-minute session. Analysis in three patients showed that reaction time (RT) variance increased over total behavioral task time, consistent with cognitive fatigue effects. In one specific patient with recordings from left and right anterior cingulate cortex, lateralized

differences in NE and SE were observed. Furthermore, NE varied as a function of RT, suggesting hemisphere-specific and monoaminergic-specific contributions to modulation of cognitive fatigue. These results align with behavioral pilot data showing that subjects who consumed caffeine did not show a comparable increase in RT variance. These findings demonstrate the feasibility of real-time, intracranial monoamine monitoring in the awake, conscious human brain under a cognitive load. The observed fluctuations in NE and SE suggest a dynamic, neuromodulatory basis for cognitive fatigue and sustained attention. Future work will expand this approach to larger samples and explore modulation of these pathways.

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## **Poster**

### **PSTR240: Imaging Human Attention**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR240.02/KK5

**Topic:** H.03. Motivation

**Support:** Honda R&D Co., Ltd.  
: NTT DATA INSTITUTE OF MANAGEMENT CONSULTING, Inc.  
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**Title:** Causal role of the ventral midbrain on sustained attention: an fMRI neurofeedback study

**Authors:** \*A. SHIINA<sup>1</sup>, S. K. SUGAWARA<sup>2</sup>, N. USUDA<sup>2</sup>, S. LIN<sup>2</sup>, J. OKUMA<sup>1</sup>, Y. UEDA<sup>1</sup>, Y. HOSHI<sup>1</sup>, M. NISHIJIMA<sup>1</sup>, M. MOMOKI<sup>3</sup>, T. IBARAKI<sup>3</sup>, M. HOSHINO<sup>1</sup>, Y. NISHIMURA<sup>2</sup>;

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**Abstract:** The ventral midbrain (VM), rich in dopaminergic neurons, widely innervates diverse cortical regions involved in various cognitive functions. Previous studies have reported that external rewards, known to activate the VM, enhance sustained attention. However, the causal role of VM activity in modulating sustained attention remains unclear. Therefore, this study aimed to investigate whether VM activity causally influences sustained attention using functional magnetic resonance imaging (fMRI) neurofeedback. Forty-six healthy volunteers participated. They performed the gradual onset continuous performance test (gradCPT) with fMRI neurofeedback in a 3T MRI scanner. The paradigm comprised three consecutive periods: resting, induction, and gradCPT. To compare the effect of VM activity on sustained attention, two induction conditions were set: up-regulation or maintenance of VM activity. Participants voluntarily controlled their VM activity via real-time visual feedback of fMRI-measured VM activity during the 20-s induction period. Following the induction period, they performed the 40-s gradCPT. This task required continuous monitoring of alternating city and mountain scenes,

each presented for 800 ms. Participants pressed a button as quickly as possible for city scenes and withheld responses for mountain scenes. Previous studies define the coefficient of variability (CV) of reaction times for city scenes as a proxy for sustained attention. A lower CV indicates better sustained attention. VM activity during the induction period was significantly higher in the up-regulation condition than in the maintenance condition, confirming successful voluntary control of the VM activity via fMRI neurofeedback. Crucially, the CV of reaction times during the gradCPT was significantly lower after the up-regulation condition than after the maintenance condition. Furthermore, regions of the dorsal and ventral attentional networks, specifically the bilateral middle and inferior frontal gyri, bilateral anterior insular cortex, and bilateral intraparietal sulcus, showed more prominent activity during the gradCPT subsequent to the up-regulation condition compared to the maintenance condition. These findings strongly suggest that enhanced VM activity causally facilitates dorsal and ventral attentional networks, thereby improving sustained attention.

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## **Poster**

### **PSTR240: Imaging Human Attention**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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**Topic:** I.01. Attention

**Support:** NSTC: 113-2410-H-A49-066-MY2  
NSTC: 112-2926-I-A49A-502-G  
NSTC 112-2321-B-A49-008-, 113-2321-B-A49-015

**Title:** Excitatory Neurometabolic Signatures of Sustained Attention in the Human Visual Cortex

**Authors:** S. N. LIN<sup>1</sup>, I. LEE<sup>2</sup>, R.-R. KUO<sup>2</sup>, C.-P. LIN<sup>3</sup>, \***L.-H. CHANG<sup>4</sup>**;

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**Abstract:** Sustained attention, involving the maintenance of both external and internal focus over time, is essential to effective perception and learning. Numerous studies have revealed distributed brain networks supporting sustained attention, including prefrontal, cingulate, thalamic, and visual cortices. While recent studies have highlighted the involvement of the visual cortex in early-stage attention modulation, its underlying neurochemical mechanisms remain insufficiently understood. Our prior work has demonstrated that excitatory neurotransmitters, particularly glutamate (Glu) and the combined glutamate-glutamine signal (Glx) play a critical role in perceptual learning—a process that typically requires prolonged and focused attentional engagement. Here, we applied time-resolved functional magnetic resonance spectroscopy (fMRS) at 3T to test whether sustained attentional demands modulate Glx levels in the visual cortex. Five healthy adults underwent three noontime sessions across consecutive days using a block design with alternating rest and visual stimulation. A vigilance task during central fixation ensured continuous attentional engagement throughout the experiment. Four spectra were acquired with the PRESS sequence (TR = 2s, TE = 30 ms, 160 time points) yielding 40 time-resolved data points (temporal resolution = 32s) per session. Spectral quality was controlled by excluding any with CRLB >15%. Attention performance was quantified by response accuracy in the vigilance task. Time-resolved analysis revealed significantly elevated Glx concentrations during stimulation blocks compared to rest blocks ( $F(443)=24.01, p<0.001$ ), with no significant change in GSH, NAA, or creatine. In contrast, time-averaged spectra (temporal resolution = 320s) failed to capture this effect. Notably, Glx concentrations showed a significant positive correlation with attentional performance ( $r=0.59, p=0.041$ ). These findings demonstrate that Glx levels in the visual cortex are dynamically modulated by visual stimulation, and that the magnitude of these changes is further influenced by attentional demands. These results suggest a potential link between attention-driven Glx modulation and early sensory processing mechanisms, possibly contributing to perceptual learning.

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**Topic:** I.01. Attention

**Support:** NIH F32 AG058479  
NIH R01 AG066430

**Title:** Locus coeruleus activity during an attention and memory task is greater in females than males

**Authors:** \*E. RILEY<sup>1</sup>, A. K. ANDERSON<sup>2</sup>, E. D. DE ROSA<sup>1</sup>;

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**Abstract:** Introduction: Sex differences in the locus coeruleus (LC) may be significant for cognition, as sex influences both its structure and function. We have found that females have stronger neuromelanin-associated MRI intensity in the LC (Riley et al., 2025), and others have identified greater dendritic density and more synapses compared to males, driven by estradiol during development (Ycaza Herrera et al., 2019). This enhances sensitivity to corticotropin-releasing factor, making female LC neurons more responsive to stress (Curtis et al., 2006). These differences may affect cognitive processes such as attention and memory (Sara & Bouret, 2012).

Methods: We examined 71 participants (64% women) aged 19-86. Participants did an attention task in a 3T GE Discovery MRI scanner: they were asked to remember a series of pictures for a later test (2-alternative forced choice, immediately after scanning) while simultaneously performing a go-nogo auditory discrimination task. We collected neuromelanin-sensitive T1-weighted turbo spin echo to identify the LC (as per our published protocol (Turker et al., 2021)), and multi-echo echo planar imaging (EPI) during the task (TR = 2,500 ms; TEs = 12.3, 26.0, and 40.0 ms; 3.0 mm isotropic voxels). Preprocessing and estimated hemodynamic responses to each trial type were done using AFNI.

Results: There was no effect of sex on the go-nogo auditory discrimination task (F ratio = 0.084,  $p = 0.77$ ) or the subsequent memory test (z value = -0.41,  $p = 0.68$ ). However, there were strong differences in LC activity during the task. We constructed a model on BOLD response (% signal change), including main effects of sex, task trial type, and timepoint (10 over 25 s), and found a main effect of sex ( $F(1,529.2) = 5.26$ ,  $p = 0.02$ ) and an interaction between sex and trial type ( $F(2,12878) = 10.98$ ,  $p < 0.00001$ ) with males having significantly smaller responses to target trials than females. We have previously found that LC responses are significantly larger for subsequently remembered compared with subsequently forgotten targets. To test whether this effect was present in males, we constructed a model on LC BOLD target response area under the curve in males with a main effect of subsequent memory and random intercepts for participants. In males, there was no significant effect of subsequent memory ( $t = 1.53$ ,  $p = 0.14$ ). In females, however, the effect was significant ( $t = 2.15$ ,  $p = 0.037$ ).

Conclusions:

This study highlights significant sex differences in LC activity during an attentional boost effect task, and in the association of LC with memory encoding, despite equivalent behavioral performance between males and females.

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**Poster**

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**Topic:** I.01. Attention

**Support:** NIH grant R01 MH132635  
R21 MH130924

**Title:** Neural Correlates of Attentional Control: Localizing Locus Coeruleus Activity with fMRI and Pupillometry

**Authors:** \*A. COOPER<sup>1</sup>, K. A. D'ARDENNE<sup>1</sup>, I. FARNSWORTH<sup>2</sup>, J. BORDEN<sup>2</sup>, S. VELIGATI<sup>2</sup>, C. S. CARTER<sup>3</sup>, J. B. SCHWEITZER<sup>2</sup>, S. M. MCCLURE<sup>1</sup>;  
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**Abstract:** Attentional control is the ability to regulate one's focus and attention towards relevant stimuli and ignore irrelevant competing stimuli. It is a critical component of cognitive control and is implicated in various mental health disorders, including attention-deficit hyperactivity disorder (ADHD), anxiety disorders, and schizophrenia. Research on attention and arousal has implicated the brainstem locus coeruleus (LC) in these processes. The LC contains norepinephrine (NE)-synthesizing neurons that play a role in attention, arousal and stress responses. However research on the LC-NE system in humans is lacking because of difficulties in recording BOLD responses in the LC due to its small size and close proximity to the fourth ventricle. We used high-resolution imaging and neuromelanin sensitive images for within-subject LC localization to improve experimental techniques to record LC BOLD activity using fMRI. To give specificity to our results, we utilized modafinil, an FDA-approved psychostimulant, to localize BOLD responses in the LC. Participants completed two experimental sessions, one on modafinil, and the other off modafinil. While in the MRI scanner, participants completed an oddball task, a paradigm used to investigate mechanisms of human attention. Neuromelanin sensitive images were used for within-subject LC localization and pupillometry data were collected in the scanner to test for a correlation with LC BOLD response amplitude. These data were used to evaluate the hypothesis that LC activity is related to performance on sustained attention tasks. This work demonstrates the utility of direct measurement of a brain structure crucial in attentional control.

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**Poster**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR240.06/KK9

**Topic:** I.01. Attention

**Support:** Institutional support

**Title:** Emotional Valence Dependent Effects of Spatial Attention on Pupil Response

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**Abstract:** Emotion perception is accomplished via coordinated activity across multiple brain networks that includes amygdala, fusiform face area (FFA), dorsal frontoparietal network, and locus coeruleus (LC). Amygdala and FFA are involved in emotion perception, contributed by frontoparietal networks known for attentional processing. LC, in addition to being a major hub for production of norepinephrine, plays a significant role in attention and arousal. Being a part of the autonomic nervous system, LC controls pupil diameter, also known to be influenced by cognitive processes like attention, memory, decision making to name a few. Recent studies have shown that spatial attention modulates pupil diameter. This study investigates whether the influence of spatial attention on pupil response is also dependent on the valence of the emotional stimuli? Pupil responses were recorded from 26 participants while they performed an emotional detection task using Posner's paradigm for the three expressions; Happy, Angry and Neutral. Spatial attention was tested at four eccentricities ( $0^\circ$ ,  $4^\circ$ ,  $8^\circ$ ,  $16^\circ$ ) with reference to the center of the monitor. A distinct pupillary response marked by constriction of pupil from the baseline was observed approximately 500 ms after stimulus onset followed by a dilation of pupil to the baseline level. Six features: constriction onset, pre-constriction dilation peak, constriction rate, constriction amplitude, latency to maximum constriction, and dilation rate were extracted from the pupillary response to analyse the data. Primarily it was observed that across emotions, constriction amplitude was greater in the valid than the invalid trials. This difference was maximum at  $0^\circ$  and  $4^\circ$  eccentricities and reduced for farther eccentricities ( $8^\circ$  and  $16^\circ$ ). Angry expression evoked a significantly smaller constriction amplitude as compared to neutral and happy expressions in the valid trials. However no differences in the amplitude was observed for the invalid trials, although the trend of constriction amplitude was same as the valid trials. The constriction amplitude regardless of emotion was inversely proportional to the eccentricities. These results provide insights into the interaction of valence and spatial attention in modulating pupil responses.

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**Poster**

**PSTR240: Imaging Human Attention**

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**Program #/Poster #:** PSTR240.07/KK10

**Topic:** I.01. Attention

**Support:** Friends of BrainHealth

**Title:** Effects of valence, arousal, and individual differences in an emotional stroop task: an fMRI study



**Authors:** \***S. RODRIGUEZ**<sup>1</sup>, G. BATCHALLI MARUTHY<sup>3</sup>, S. TRIVEDI<sup>2</sup>, B. P. RYPMA<sup>4</sup>;  
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**Abstract:** Emotional words have been used to study the impact of affective stimuli on attention and executive control processes. The emotional Stroop (eStroop) task provides insight into how individuals process conflicting emotional stimuli and how such stimuli modulate neural activity. We examined Blood Oxygen Level Dependent (BOLD) signal differences across four emotional-word conditions and investigated practice-related changes in reaction times (RTs). We hypothesized that each condition would elicit distinct BOLD responses, reflecting neural processing based on the emotional valence and arousal of the stimuli. Forty-three healthy participants (age 19 - 31 years; 25 males) performed the eStroop task during BOLD scanning. Participants were to identify the font color of emotional words via button-press as quickly and accurately as possible, while ignoring their semantic content. Functional MRI data were acquired using a 3T Siemens MAGNETOM Prisma scanner. Each participant completed three runs of 150 trials. Words were drawn from a standard database and categorized into five different emotional word conditions: (1) negative-valence high-arousal (NH), (2) negative-valence low-arousal (NL), (3) positive-valence high-arousal (PH), (4) positive-valence low-arousal (PL), and (5) neutral (Neu) words. Interference was measured by the RT difference between emotional and neutral words. Preliminary analyses demonstrate individual differences in emotional interference during the task. Mean RTs were similar across conditions, but the subtractive contrasts (e.g. PH-Neu, NL-Neu) revealed individual variability in emotional interference. For instance, the PH-Neu contrast ranged from -83.57ms to 98.59ms, indicating that for some participants high-valence and arousing words interfered with their color-naming performance, whereas other words facilitated color-naming performance. Furthermore, in some contrasts, a subset of participants showed facilitation in Run 1, a mix of interference and facilitation in Run 2, and interference in Run 3. Another subset of participants showed interference in Run 1, a mix of interference and facilitation in Run 2, and facilitation in Run 3. This divergence reflects significant individual variability, probably driven by distinct underlying neural mechanisms. A repeated-measures ANOVA revealed condition effects on BOLD signal in several brain regions ( $p < .05$ ), suggesting that emotional stimuli elicit distinct attention processes and neural activity patterns depending on their valence and arousal characteristics.

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**Program #/Poster #:** PSTR240.08/KK11

**Topic:** I.01. Attention

**Support:** T2421004

**Title:** Attention modulates the spatial representation of face ensembles

**Authors:** \*Y. DANDAN<sup>1</sup>, J. LU<sup>1,2</sup>, C. MO<sup>5</sup>, B. SAYIM<sup>6</sup>, F. FANG<sup>1,2,3,4</sup>;

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**Abstract:** Ensemble perception, the ability to represent summary statistical information, such as the average and variance, from a group of similar objects, is a crucial mechanism for overcoming the limitations of visual processing. However, it remains unclear how exactly the visual system integrates information from local elements distributed across the visual field to form an ensemble representation. Here, we employed a concurrent psychophysics-fMRI experiment to investigate the spatial representations of individual items under varying task demands and levels of categorical congruency. The stimuli consisted of a central face surrounded by eight faces with varying emotions. In three attentional allocation conditions, participants were required to report the central face's emotion ('Central' task), the perceived ensemble ('Ensemble' task), or to ignore the fixated central face and report the ensemble of surrounding faces ('Surrounding' task). The emotional valence of the central face and the surrounding faces ('flankers') was either categorically congruent or incongruent. Since the same stimuli were used in all three conditions, we were able to isolate changes in the neural stimulus representations across regions of interest (ROIs) induced by task demands. The preliminary results revealed an interaction between task demands and categorical congruency. When the central face and the flankers were categorically congruent, performance was comparable across all three task conditions. However, with categorically incongruent stimuli, performance in the Ensemble task was significantly impaired compared to the Central and Surrounding tasks. The interaction emerged as early as V1, and extended through early visual areas (V1-V3). In the Central task, task-irrelevant items located in the periphery barely elicited additional brain activation. In the Ensemble task, when both foveal and peripheral items were task-relevant, activation was higher for items in the fovea and in the periphery (especially along the horizontal and vertical axes) compared to the average activation across all nine items. Importantly, in the Surrounding task, where the foveal item was task-irrelevant, overall brain activation was elevated for incongruent compared to congruent foveal faces and flankers. These findings show that task demands and attentional allocation strongly modulated brain activity. We suggest that selective attending to peripheral stimuli while ignoring foveal input requires a cognitive cost but can be accomplished during ensemble perception.

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**Poster**

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**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR240.09/KK12

**Topic:** I.01. Attention

**Title:** Effect of premenstrual syndrome on emotional regulation, attention and memory

**Authors:** \*S. QUIÑONES BELTRAN<sup>1</sup>, L. LLAMAS-ALONSO<sup>1</sup>, J. RAMOS-LOYO<sup>2</sup>;

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**Abstract:** Premenstrual Syndrome (PMS) is a common phenomenon in the lives of women of reproductive age, characterized by emotional, behavioral, and somatic symptoms occurring during the late luteal phase of the menstrual cycle. The presence of these symptoms can interfere with personal, academic, or professional well-being. To mitigate its effects, women often develop various emotional regulation (ER) strategies aimed at adaptively modulating emotions. This study aimed to identify whether PMS has an effect on selective attention and recognition memory for emotional images previously presented in an explicit ER task. A total of 33 control women and 37 women with PMS were evaluated. All participants received brief training on the cognitive reappraisal ER strategy, with instructions to change the meaning of emotional stimuli and reinterpret them in a positive light. Subsequently, they applied this strategy to 10 neutral, 10 pleasant, and 10 unpleasant stimuli. These stimuli were later used as targets in an oddball attention paradigm, mixed with 70 new stimuli. Finally, two weeks later, participants completed a recognition memory task in which they had to identify the target stimuli from among a new set with similar characteristics. 2x3 ANOVAs were conducted for behavioral performance measures. Faster attention reaction times were observed in response to unpleasant stimuli, although no differences were found in the number of correct responses. Better recall was found for unpleasant stimuli compared to neutral and pleasant ones. Ultimately, no differences were found as a function of premenstrual symptomatology. The results suggest that the explicit ER strategy mitigated the deleterious effects of PMS, particularly in response to unpleasant information, thus enabling similar performance between women with and without PMS symptoms.

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**Program #/Poster #:** PSTR240.10/KK13

**Topic:** I.01. Attention

**Title:** Effects of subliminal phobic stimuli on antisaccade performance and ERP responses to fearful faces

**Authors:** \*V. HUERTA<sup>1</sup>, J. RAMOS-LOYO<sup>2</sup>;

<sup>2</sup>Inst. de Neurociencias, <sup>1</sup>Univ. de Guadalajara, Guadalajara, Mexico

**Abstract:** Pre-conscious detection of phobic stimuli can activate early threat-detection systems, increasing inhibitory demands and contributing to the hypervigilance-avoidance cycle. This study examined whether subliminal images of cockroaches modulate oculomotor behavior and event-related potentials (ERPs) in women with specific phobia. Forty-four women (22 phobic, 22 control; 18-35 years) completed a pro-/antisaccade task involving subliminal images (cockroach or plate), a central directional cue, and a peripheral face (neutral or fearful). Eye movements and 32-channel EEG were recorded. Three-way mixed ANOVAs were applied to behavioral and ERP data, including channel as a within-subject factor in ERP analyses. At the behavioral level, In antisaccade trials, subliminal cockroach images increased the proportion of correct responses relative to plates ( $p = .01$ ), suggesting enhanced inhibitory control. Fearful faces lengthened saccade onset latency ( $p = .04$ ) and reduced peak velocity ( $p = .01$ ) only in antisaccades, indicating greater cognitive load during response suppression under emotional salience. In prosaccades, fearful faces increased peak velocity ( $p = .01$ ), possibly reflecting enhanced motor readiness driven by arousal. No group effects were found in eye-movement measures. ERP analyses revealed that, at occipital sites, the phobic group showed larger N1 amplitudes to fearful faces ( $p = .02$ ), consistent with early visual hyperresponsivity. P2 amplitudes at Oz were also higher in phobics, particularly when subliminal cockroach images preceded fearful faces ( $p = .04$ ), suggesting amplified perceptual integration of emotionally salient stimuli. In prosaccades, phobic participants showed increased N2 at frontal regions, reduced P3 amplitudes to fearful faces, and diminished parietal LPP ( $p = .05$ ), indicating heightened conflict monitoring but blunted evaluative processing. In antisaccades, phobics exhibited enhanced N2 at frontocentral regions and reduced P3 and LPP amplitudes ( $p = .05$ ), particularly when fearful faces followed subliminal cockroach images. These findings indicate that subliminal exposure to phobic stimuli can modulate early perceptual processing and late evaluative stages, especially in emotionally charged antisaccade contexts. The altered neurocognitive pattern in phobics, marked by early hyperresponsivity and reduced late-stage engagement, suggests a dysfunctional cascade of visual and cognitive processes that may sustain avoidance and threat sensitivity despite unaltered overt behavior.

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**Poster**

**PSTR240: Imaging Human Attention**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR240.11/KK14

**Topic:** I.01. Attention

**Support:** NIH U01DA041174

**Title:** Dissimilarity in neural representations of emotional categories is associated with greater attention problems in youth

**Authors:** \*Y.-C. LIN<sup>1</sup>, Q. MENG<sup>1</sup>, E. MUSSER<sup>1</sup>, D. G. GEE<sup>2</sup>, A. BASKIN-SOMMERS<sup>2</sup>, B. CASEY<sup>1</sup>;

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**Abstract:** Defining characteristics of Attention-Deficit/Hyperactivity Disorder (ADHD) include inattention, impulsivity, and hyperactivity. Yet, there is evidence of heightened emotional sensitivity and reactivity in these individuals suggesting that deficient emotional self-regulation is an important component of ADHD. Here, we investigate emotional sensitivity in youth with attention problems by examining dissimilarity in their neural representations of emotional categories during a cognitively demanding task. We hypothesized that youth with more attention problems would show more distinct neural representations between emotional categories than those with fewer attention problems and that this pattern would be associated with diminished cognitive performance. To test these hypotheses we utilized neuroimaging and behavioral data from the Adolescent Brain Cognitive Development Study<sup>SM</sup> Release 4.0 (11-12 year-old; n=4953 after quality control). Attention problems were assessed using the Child Behavior Checklist (Achenbach & Rescorla, 2001). Participants performed an n-back working memory task in the scanner that included 3 emotional categories (happy, fearful, and neutral faces) and high (2-back) and low (0-back) memory loads (Casey et al., 2018). Representational similarity analysis was used to examine dissimilarities in neural representations of emotional face categories. Neural dissimilarity of 7 functional networks (Yeo et al., 2011) were calculated by Pearson correlations of beta weight contrasts between the three emotional categories. The associations between dissimilarity, attention problems, and task performance were tested using mixed-effect linear models. Youth high in attention problems performed worse than those low in attention problems on both the 0-back ( $p < .001$ ) and 2-back conditions ( $p < .001$ ). Consistent with our hypothesis, youth with more attention problems showed greater dissimilarity between emotional categories, that differed by memory load and network. Specifically, for the low memory load condition only neural dissimilarity in the visual network was associated with attention problems. However, in the more demanding high load memory condition, dissimilarity in all 7 networks was associated with more attention problems with the ventral attention network showing the largest effect (marginal  $R^2 = 0.05$ ). Our results suggest that heightened sensitivity to emotional information during challenging task conditions may diminish cognitive performance. These findings provide further evidence of a role of emotional sensitivity and/or dysregulation in youth with attentional problems like those with ADHD.

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**Poster**

**PSTR240: Imaging Human Attention**

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**Program #/Poster #:** PSTR240.12/KK15

**Topic:** I.01. Attention

**Support:** NIH 5T32HD007009  
National Science Foundation BCS 2043740 (MDR)

**Title:** Characterizing associations between environmental exposures, attention problems, and attention-related brain networks in youth

**Authors:** \*N. BERRIAN<sup>1</sup>, A. S. KELLER<sup>4,5</sup>, A. CHAO<sup>1</sup>, A. J. STIER<sup>6</sup>, O. KARDAN<sup>7</sup>, R. BARZILAY<sup>8</sup>, M. G. BERMAN<sup>2</sup>, M. D. ROSENBERG<sup>3</sup>;  
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**Abstract:** The ability to sustain attention varies between individuals and changes across the lifespan. Attentional impairments are associated with broad effects, from poor school performance to incidence of psychiatric disorders. Individual differences in sustained attention are linked to variability of large-scale functional brain networks as well as environmental factors such as pre-/perinatal events, socioeconomic status, and toxin exposure. Although these environmental exposures are recognized as crucial influences on cognitive development, the underlying neural mechanism by which they affect attention is unclear. Here, we test the hypothesis that multidimensional environmental exposures are related to behavioral and neural signatures of attentional functioning in adolescence. To do so, we analyzed data from the Adolescent Brain Cognitive Development Study™ (N = 2286), which includes resting-state fMRI, variables related to cognition, and youths' social and physical environments. Results revealed that a measure of multidimensional environmental experience, or the "exposome" (Keller et al., 2024; Moore et al., 2022), predicted youths' attention problems as reported by their caregivers at age 9-10 and 11-12 years. Exposome scores were negatively associated with household income, such that youth from wealthier backgrounds have lower exposome scores and fewer attention problems. To capture brain networks supporting attention, we utilized a whole-brain functional network model whose strength predicts individuals' sustained attention performance, the sustained-attention Connectome-based Predictive Model (saCPM; Rosenberg et al., 2016). Mixed effects models revealed that exposome scores are significantly associated with saCPM network strength, even after accounting for age, sex, head motion, and number of scans. Youth with higher exposome scores expressed functional connectivity signatures of worse sustained attention at rest at age 9-10 and 11-12. At age 9-10, causal mediation analysis revealed that saCPM network strength significantly mediated the association between exposome score and CBCL-APS score. Together, our results suggest that multidimensional environmental exposures predict attentional functioning and underlying functional brain network architecture in youth.

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**Poster**

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**Program #/Poster #:** PSTR240.13/KK16

**Topic:** I.01. Attention

**Support:** P50MH132642  
RO1 EY017699  
R01MH137624

**Title:** Thalamocortical connectivity during attention under perceptual uncertainty

**Authors:** \*X. LIU<sup>1</sup>, X. LIU<sup>3</sup>, K. N. KAY<sup>5</sup>, S. KASTNER<sup>2</sup>, M. J. ARCARO<sup>4</sup>;  
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**Abstract:** Previous animal studies and human fMRI resting-state data have revealed extensive reciprocal connections between higher-order thalamic nuclei, such as pulvinar (PUL) and mediodorsal nucleus (MD), and widespread cortical regions including visual cortex and the fronto-parietal network (FPN), positioning it in a strategic place to influence cognitive control functions (Arcaro et al., 2015; Halassa & Kastner, 2017). However, it remains unclear whether and how thalamocortical connectivity modulates behavior when cognitive control demands vary. Here, we designed an fMRI experiment that combined elements of perceptual decision making and spatial attention. On each trial, participants maintained central fixation while viewing two gratings presented in the periphery on either side of fixation. A central cue consisting of a cloud of red and blue dots indicated the likely location of an upcoming target with 80% validity. Cue uncertainty was manipulated by varying the red-blue ratio. After a variable delay, a brief near-threshold orientation change appeared at one grating. Participants reported the location of change, then rated their confidence in the cue on a five-point scale. When cue uncertainty was low, there was a significant lateralization effect during the delay period in early visual cortex and intraparietal sulcus, with greater activation contralateral to the cued location. This effect diminished as cue uncertainty increased, paralleling the decline in the behavioral endogenous attention effect. Pulvinar activity reflected distinct task phases: ventral PUL was active during cue presentation, while lateral dorsal PUL was active during the delay period when attention was deployed. Using GLMSingle (Prince et al., 2022), we extracted single-trial beta weights and computed the fingerprint functional connectivity between cortical and thalamus ROIs for different components of the task. Preliminary results reveal increased lateral dorsal PUL-FPN connectivity in the right hemisphere during attention towards the contralateral hemifield. We predict that 1) PUL-FPN connectivity will decrease with increasing uncertainty, tracking perceptual confidence, and 2) MD-PFC connectivity will increase as cognitive control demands increase. In summary, our results suggest that thalamocortical interactions adaptively support perceptual decision-making in response to varying cognitive control demands.

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**Program #/Poster #:** PSTR240.14/KK17

**Topic:** I.01. Attention

**Support:** NIH Grant RO1 MH117991

**Title:** Observation of an Attention Template in the Dorsal Attention Network in Feature-based Visual Attention

**Authors:** \*S. MEYYAPPAN<sup>1</sup>, M. DING<sup>2</sup>, G. R. MANGUN<sup>3</sup>;

<sup>1</sup>Univ. of California Davis, Davis, CA; <sup>2</sup>Univ. Florida, Gainesville, FL; <sup>3</sup>Ctr. for Mind and Brain, Univ. of California, Davis, Davis, CA

**Abstract:** Attention can be either drawn reflexively based on the salience of the external sensory event (bottom-up) or directed voluntarily (top-down) based on behavioral goals. During voluntary attention, an attention-directing cue, is posited to engage top-down processes to instantiate an internal representation resembling the features of the anticipated target. This representation, also known as attentional template, is expected to guide attentional selection through a mechanism known as template matching. While the notion of an attention template has been frequently invoked in behavioral studies, direct neural evidence for their existence has been limited. We addressed this problem by recording fMRI data from 20 subjects performing a cued feature-based attention task. Each trial began with an auditory cue, which directed subjects to attend to a color (red or green). Following a random time delay, two rectangles, one red and one green, were displayed in the right and left visual field. The subjects were required to discriminate the orientation (vertical or horizontal) of the rectangle matching the cued color. Applying multivoxel pattern analysis (MVPA) to the fMRI data from the dorsal attention network (FEF and IPS), we found that (1) cue-evoked neural activities can be decoded above chance level, suggesting that top-down attention to red vs green gave rise to different neural patterns, (2) target-evoked neural activities can be decoded above chance level, suggesting that attended red rectangle and attended green rectangle activated different neural patterns, and (3) importantly, cue-classifiers can cross-decode the target-evoked activities above chance level and the cross-decoding accuracy is positively associated with behavioral performance. These results suggest that an attention template was formed in the dorsal attention network during anticipation of stimulus processing and stronger template matching resulted in better behavioral performance.

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**Program #/Poster #:** PSTR240.15/KK18



**Topic:** I.01. Attention

**Support:** NIH R01 EY035300  
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**Title:** Neural feature dimension maps integrate relevant and salient information to guide attentional priority

**Authors:** \*D. THAYER<sup>1</sup>, T. C. SPRAGUE<sup>2</sup>;  
<sup>1</sup>Univ. of California, Santa Barbara, Goleta, CA; <sup>2</sup>Psychological and Brain Sci., UC Santa Barbara, Goleta, CA

**Abstract:** Image-salient distractors and goal-relevant targets simultaneously compete for our attention (Sprague et al., 2018). To resolve competition among items in the visual field, maps that preferentially respond to specific feature dimensions (e.g., color; motion) index salient and relevant locations based on their preferred feature within corresponding ‘feature dimension maps’, which are subsequently integrated into a feature-agnostic priority map, where the most important location guides attention (Itti & Koch, 2001; Serences & Yantis, 2006). Even though feature dimension maps play a critical role in guiding attention (Thayer & Sprague, 2023), it is unclear how activation profiles in these neural maps resolve competition between task-relevant and task-irrelevant, but salient, items. Here, participants performed a visual search task where they were cued to search for a motion- or color-defined target within an array of distracting colorful moving dot stimuli. On most trials, an additional item in the array was made salient either because it was moving in a different direction, or was presented in a different color from the rest of the search array. Thus, a salient and relevant item were simultaneously present and competing for attentional priority. We measured human fMRI data and computed spatial inverted encoding models to reconstruct maps of the visual field using neural activation patterns from feature-selective retinotopic regions (motion: TO1/TO2; color: hV4/VO1/VO2) to investigate the representation of attentional priority. We found that feature-selective regions simultaneously indexed the location of relevant and salient items throughout the visual field. Responses to these items were modulated by feature preferences—motion-selective regions preferentially responded to motion-defined target and distractors, while color-selective regions responded more to important color-defined items. Furthermore, activation profiles in motion-selective regions reflected behavior: neural responses were stronger for the target than the distractor when participants performed faster on the search task, but the neural response to targets and distractors were equivalent when responses were slower. These results suggest that responses in neural motion dimension maps capture the competition that is eventually resolved to guide attention during visual search and that responses across feature-selective regions are critical for computing attentional priority to guide behavior.

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**Poster**

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**Topic:** I.01. Attention

**Support:** NIH R01 EY035300  
URCA Grant

**Title:** Behavioral measures of salience differ between feature dimensions across levels of feature contrast

**Authors:** \*C. MELIKIAN<sup>1</sup>, D. THAYER<sup>3</sup>, T. C. SPRAGUE<sup>2</sup>;

<sup>1</sup>UC Santa Barbara, Glendale, CA; <sup>2</sup>Psychological and Brain Sci., UC Santa Barbara, Goleta, CA; <sup>3</sup>Univ. of California, Santa Barbara, Goleta, CA

**Abstract:** To navigate our dynamic environment, the brain must prioritize important stimuli. A key factor that determines stimulus importance is visual salience, which can be defined by the extent to which stimulus features (e.g., color or motion) stand out from the background. Previous human fMRI studies have shown that the level of feature contrast drives distinct patterns of activation in color (hV4/VO1/VO2)- and motion (TO1/TO2)-selective brain regions: color-selective regions index color contrast monotonically, while motion-selective regions index motion contrast with a maximal response at a moderate level of salience (Thayer & Sprague, 2023; Machinak et al., 2024). However, it is unclear whether behavioral measures of attentional selection track these divergent neural responses to feature salience. Here, we adapted the same stimuli used in previous fMRI studies to investigate whether behavioral measures of salience follow these idiosyncratic modulations of neural salience maps across feature dimensions. Participants viewed dot array stimuli with a subsection of dots made salient by parametrically manipulating either the color or motion relative to the rest of the array. In order to assess attentional capture, we measured eye movements and quantified the proportion of first fixations made to the salient location, fixation dwell time, and latency to first fixation. For both feature dimensions, as feature contrast increased, the proportion of first fixations directed toward the salient region increased. In addition, moderate levels of motion contrast elicited significantly longer dwell times than maximal motion contrast, suggesting that it may be harder to disengage attention at intermediate levels of motion salience. When directly comparing motion and color, motion directed more first fixations at moderate levels of contrast than color. The alignment between these behavioral and previous fMRI results suggests that feature-specific neural salience maps guide real-world attentional behavior, with color and motion influencing attention through distinct mechanisms.

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**Poster**

**PSTR240: Imaging Human Attention**

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**Program #/Poster #:** PSTR240.17/KK20

**Topic:** I.01. Attention

**Support:** Singapore Ministry of Education start-up  
MINDEF/SINAPSE  
DSO National Laboratories

**Title:** Characterising the modality-general and modality-specific neural mechanisms of attentional capture by surprise

**Authors:** \*E.-L. LEONG<sup>1</sup>, G. J. LIAW<sup>2</sup>, C. L. ASPLUND<sup>1</sup>;  
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**Abstract:** Unexpected stimuli can capture attention and transiently disrupt ongoing behaviour. This effect is evidenced in the surprise-induced blindness (SiB; visual modality) and surprise-induced deafness (SiD; auditory modality) paradigms, where infrequent, unexpected items impair detection of task-relevant probes presented shortly thereafter (300-400 ms). The detection deficits are substantial and habituate after repeated exposure to surprises in both modalities, often with greater initial deficits and more rapid habituation in vision. It remains unclear, however, whether a shared, modality-general mechanism underlies distraction in both modalities, or whether the deficits are better explained by modality-specific processes. To address this question, we examined the neural correlates of surprise-induced attentional capture in vision and audition. Participants (n=22) completed both SiB and SiD paradigms during functional MRI scanning. Behaviourally, robust probe detection impairments were observed in both modalities, though only the visual deficits showed clear habituation. Moreover, in a larger sample (n=64), individual differences in surprise deficits were uncorrelated between modalities. Whole-brain analyses revealed both shared and distinct neural correlates of surprise. In both modalities, surprise trials showed greater activation than control trials in the inferior frontal junction (IFJ) and temporoparietal junction (TPJ), consistent with prior SiB findings, as well as in the hippocampus. In contrast, modality-specific effects emerged in primary sensory cortices and category-selective visual regions, including the fusiform face area and parahippocampal place area. For the visual modality, activity attenuated selectively in the IFJ, TPJ, and hippocampus, mirroring the habituation of the behavioral deficits. These findings suggest that surprise-related attentional capture engages a core, modality-general attentional network, alongside modality-specific mechanisms that may account for differential habituation and the lack of performance correlations across vision and audition.

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**Topic:** I.01. Attention

**Support:** BrainWorks, Wu Tsai Institute, Yale University (RRID:SCR\_024556)

**Title:** Brain areas engaged when shifting between external and internal attention

**Authors:** \*D. GRESCH<sup>1</sup>, D. WEI<sup>1</sup>, A. NOBRE<sup>2</sup>;

<sup>2</sup>Dept. of Psychology, <sup>1</sup>Yale Univ., New Haven, CT

**Abstract:** During natural behavior, attention shifts seamlessly between information in the external environment and internal representations held in memory. Only recently has research begun to investigate these dynamic shifts between external and internal attention using behavioral, eye-tracking, and electrophysiological measures. These studies have revealed behavioral differences accompanied by distinct neural patterns: differentiation between within- and between-domain shifts emerges early, evolves dynamically over time, and is broadly distributed across the scalp, suggesting the involvement of multiple processing stages within distributed networks as attention moves between perceptual and mnemonic domains. To determine which neural systems are recruited during such between-domain shifts, we conducted an event-related functional magnetic resonance imaging study using a recently developed task that combines perceptual and working-memory components. In this task, participants were presented with two consecutive cues, sequentially guiding attention to encoded contents, upcoming sensory input, or both. Crucially, the second cue could either shift spatial attention within the same domain (internal-to-internal or external-to-external) or shift spatial attention between domains (external-to-internal or internal-to-external). This design allowed for the systematic investigation of attentional shifts both within and between perception and working memory, as well as direct comparisons of the neural systems engaged in orienting external and internal attention. Consistent with previous work, both external and internal shifts of spatial attention activated dorsal frontoparietal regions, with internal shifts additionally recruiting posterior parietal and lateral and medial prefrontal areas. Shifting attention between the perceptual and working-memory domains modulated brain activity more subtly, warranting further analysis to elucidate the specific roles of brain regions during between-domain shifts.

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**Support:** NSF Grant BCS-2122866  
NIH Grant T32EY014536

**Title:** Shifts of object-based and spatial attention can be decoded from spatiotemporal activation patterns in posterior parietal cortex

**Authors:** \*D. H. HUGHES, A. S. GREENBERG;  
Biomed. Engin., Med. Col. of Wisconsin, Milwaukee, WI

**Abstract:** Shifts of attention in multiple domains (e.g., object, spatial, feature) are controlled by overlapping populations of neurons, each tuned to a preferred domain. We previously showed that spatial- and feature-tuned populations colocalize to posterior parietal cortex (PPC), leading to above-chance decoding of shift domain in this region. Conversely, frontal control regions lacked information regarding shift domain, yielding chance-level decoding. Here, we compared spatial and object-based attention shifts to determine the domain generality of these brain regions. We positioned 2 RSVP streams of overlapping face and house stimuli to the left and right of fixation. The stimuli were embedded in noise and gradually changed each second. A symbolic cue appeared every 3, 6, or 9 s, indicating which stream participants should attend (e.g., left face). The cues resulted in the following attentional actions: shift object, shift space, shift both, or hold. Participants (n = 9) detected a specific face and a specific house appearing in the attended stream one or two seconds after the onset of a subset of cues. Participants completed at least seven runs of the task during fMRI. Using these data, we calculated a group-level conjunction to identify brain areas that were active for all three shift types, revealing regions of interest (ROIs) in bilateral PPC and left frontal eye fields. Next, we trained a support vector machine on the spatiotemporal patterns of activation (-2 to 12 s relative to cue onset) in these ROIs and observed above-chance decoding in PPC when comparing object and spatial shifts. To investigate the relationship between all three shift types, we applied multidimensional scaling to the spatiotemporal activation patterns in PPC for shifts and holds. We then calculated the vectors for shift object, shift space, and shift both in this common space, using the hold condition as a common reference. Finally, we calculated the angle between each pair of vectors. The angle between shift object and shift location remained  $\sim 90^\circ$  for the entire period. The angle between shift object and shift both was anticorrelated with the angle between shift space and shift both; with both angles fluctuating between  $130 - 150^\circ$  until seven seconds post-cue, at which point they diverged. The angle between shift object and shift both fell to  $\sim 90^\circ$  from 7 to 12 s post-cue onset, while the angle between shift space and shift both rose to  $\sim 180^\circ$ . Together, these results support the theory of overlapping, independent neural populations with a shift-domain preference in PPC. Furthermore, the “shift both” action is likely supported by both of these populations rather than a unique population of neurons.

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**Poster**

**PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.01/LL1

**Topic:** I.03. Decision Making

**Title:** Delay discounting in NrCAM deficient mice under acute and chronic stress: beneficial effects of NMDA antagonist MK801

**Authors:** \*C. V. BUHUSI, M. BUHUSI;  
Psychology, Utah State Univ., Logan, UT

**Abstract:** Stress significantly impacts executive functions, often increasing impulsive, emotion-driven and risk-taking choices and decreasing cognitive and behavioral flexibility and ability to adapt to a changing environment. Recent studies have revealed links between stress hormones and changes in the expression of numerous gene transcripts. An emerging candidate gene related to vulnerability to stress and psychopathology is the neuronal cell adhesion molecule (NrCAM)(Olsen et al., 2022). NrCAM is widely expressed and has important physiological functions in the nervous system across the lifespan, from axonal growth and guidance to spine and synaptic pruning, to organization of proteins at the nodes of Ranvier. Here we investigated decision making in NrCAM-deficient mice (KO) and their wild-type (WT) littermates under acute and chronic stress, using a Delay Discounting (DD) paradigm (Buhusi et al., 2016.) Mice were trained and tested in the DD paradigm under no stress, acute social stress, and chronic unpredictable stress conditions. Since chronic stress is known to induce inhibition-excitation imbalances and alterations in NMDA receptor expression in brain areas involved in executive functions, mice were then tested under systemic (i.p.) administration of NMDA antagonist MK801 (0, 0.03, 0.1 mg/kg) or AMPA antagonist CNQX (0, 1.8, 5.6 mg/kg). The discounting curves were normalized (Myerson et al., 2001) and the normalized % Area Under the Curve (AUC) was computed and analyzed: a small %AUC was taken to be indicative of choice impulsivity. NrCAM KO and WT mice discounted similarly under no stress conditions, but WT mice became more impulsive than NrCAM KOs both after acute ( $p<0.01$ ) and chronic stress ( $p<0.05$ ). CNQX increased impulsivity in WT but not in NrCAM KO mice ( $p<0.05$ ). In contrast, MK801 decreased impulsivity ( $p<0.01$ ) and increased response omissions in NrCAM KO mice ( $p<0.01$ ) but not in WT mice. In contrast to a previous study suggesting increased motor impulsivity in NrCAM-deficient mice (Matzel et al., 2008), in our study NrCAM deficiency seems to mitigate the effects of stress on choice impulsivity. Pharmacological manipulations support a differential role of NMDA and AMPA receptors in the DD paradigm, with beneficial roles of low-dose MK801 in reducing impulsive choice in NrCAM-deficient mice. Taken together, our results further support poor performance in various decision making tasks under stress and a link between NrCAM and vulnerability to stress-induced cognitive and behavioral dysfunctions.

**Disclosures:** C.V. Buhusi: None. M. Buhusi: None.

**Poster**

**PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

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**Topic:** I.03. Decision Making

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**Title:** Targeting clozapine responsive cells ameliorates noisy decision making in a schizophrenia mouse model

**Authors:** \*Y. IINO, C. SHIMIZU, S. SHI;  
Univ. of Tsukuba, Tsukuba, Japan

**Abstract:** Clozapine is considered the most effective antipsychotic for treatment-resistant schizophrenia, yet its precise mechanism of action remains unclear. Here, we combine single-cell transcriptomics, pharmacological modeling and behavioral experiments to identify and validate a population of clozapine-responsive cells underlying its therapeutic effects. First, by integrating clozapine's receptor binding affinities with mouse and human single-cell RNA sequencing data, we constructed a mathematical model to predict neuronal populations most responsive to clozapine. This model identified a subset of pyramidal neurons with distinct receptor expression patterns in the prefrontal cortex (PFC). Leveraging this mathematical model, we performed in silico screening to identify patterns of receptor inhibition that could selectively activate these clozapine-responsive cells in the PFC. Our simulations revealed that the simultaneous inhibition of three specific receptors could potentially activate clozapine-responsive cells. To functionally evaluate these predictions, we designed behavioral experiments using a two-choice probabilistic bandit task in MK-801-induced schizophrenia mouse models. This task requires animals to balance exploitation of known high-reward options with exploration of uncertain alternatives, thereby capturing adaptive decision-making. We administered clozapine or a cocktail of receptor-selective antagonists and quantitatively analyzed behavior using reinforcement learning (RL) models, enabling us to dissociate drug effects on learning rate ( $\alpha$ ), decision stochasticity ( $\epsilon$ , behavioral noise). Clozapine and the receptor-inhibitor cocktail both reduced choice randomness (lower  $\epsilon$ ), indicating reduced cognitive noise. To causally validate the role of clozapine-responsive cells, we are conducting TRAP2-based cell tagging and selective inhibition/knockout experiments, aiming to test whether silencing these cells abolishes both the effects of clozapine and the receptor-inhibitor cocktail. Additionally, whole-brain tissue clearing and c-Fos mapping are underway to compare activation patterns with those predicted by the model. Together, our study proposes a new framework for understanding the mechanism of clozapine, integrating quantitative behavioral analysis with molecular and cellular targeting, and may suggest novel intervention strategies for treatment-resistant schizophrenia. Ongoing experiments will further clarify the causal links between clozapine-responsive cell activation and behavioral rescue.

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**Poster**

**PSTR241: Neural Mechanisms: Maladaptive Choice**

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**Program #/Poster #:** PSTR241.03/LL3

**Topic:** I.03. Decision Making

**Support:** MOST 113-2423-H-002 -010  
MOST 113-2321-B-002 -031

**Title:** Akt1 modulates parvalbumin neuron function in the dorsomedial striatum to regulate reward-based decision making in mice

**Authors:** \*J.-C. PEI, W.-S. LAI;  
Natl. Taiwan Univ., Taipei, Taiwan

**Abstract:** Cognitive deficits, including impairments in reward-based decision making, are a core feature of schizophrenia and remain difficult to treat. AKT1, a major schizophrenia risk gene, has been implicated in synaptic plasticity and neuromodulation, but its specific role in GABAergic interneurons remains underexplored. Here, we investigated the impact of AKT1 deficiency on GABAergic subtypes, particularly parvalbumin (PV) neurons, and associated behavioral phenotypes using mouse models. Akt1 heterozygous mutant mice (Akt1<sup>+/-</sup>) showed altered behavior in a probabilistic decision-making task, including increased lose-stay choices following high-reward outcomes and decreased choice consistency—suggesting impairments in outcome evaluation and reinforcement learning. These behavioral changes were accompanied by reduced neural activity in the dorsomedial striatum (DMS), a region implicated in goal-directed behavior. Immunohistochemistry revealed a region-specific reduction of PV expression in the DMS of Akt1<sup>+/-</sup> mice. Co-localization analysis further showed decreased AKT1 expression in PV-positive neurons. To test causality, we performed region-specific knockdown of Akt1 in the DMS, which replicated the behavioral alterations observed in Akt1<sup>+/-</sup> mice. Furthermore, conditional knockout of Akt1 in PV-expressing neurons, but not in GAD-expressing GABAergic neurons, led to similar deficits in decision-making behavior. Together, our findings demonstrate that AKT1 plays a critical role in modulating PV neuron function within the DMS and is essential for adaptive decision making. These results provide novel insight into how AKT1 dysfunction in specific interneuron subtypes may contribute to cognitive deficits in schizophrenia.

**Disclosures:** J. Pei: None. W. Lai: None.

**Poster**

**PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.04/LL4



**Topic:** I.03. Decision Making

**Support:** NIH R56-MH130488  
Sloan Research Fellowship

**Title:** Information Flow Underlying History-Dependent Decision Bias in the Posterior Network

**Authors:** \*Y. LEE, S. CINQUEMANI, S. KORDE, E. HWANG;  
Chicago Med. Sch., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

**Abstract:** Animals and humans frequently exhibit history-dependent biases in decision-making, which may be adaptive behavioral strategies in dynamic environments. Previous studies have identified the posterior parietal cortex (PPC) as a key region for history-dependent decision-making. Specifically, PPC neurons projecting to the striatum (PPC<sub>STR</sub>) have been implicated in encoding history-dependent decision bias. Furthermore, PPC<sub>STR</sub> neurons receive enhanced synaptic input from the cingulate cortex (CC). These findings suggest that the posterior network, comprising the CC, PPC, and striatum (STR), plays a key role in generating history bias. In this study, we investigated how this network contributes to the formation of history bias by identifying the distinct roles of each region in processing, transmitting, and integrating history information to generate history-dependent decisions. Retrograde viral tracing was used to selectively label CC neurons projecting to the PPC (CC<sub>PPC</sub>) or PPC<sub>STR</sub> neurons. The activity of these neurons was recorded through two-photon calcium imaging while mice performed a sensory-guided decision-making task. Trial-by-trial history bias was quantified using a generalized linear model that estimated the contribution of stimulus and choice-outcome history to each choice. The estimated contribution of choice-outcome history was then used as a measure of history bias. We quantified the amount of history and history-bias information in each projection neuron, revealing that CC<sub>PPC</sub> neurons encode outcome history most strongly, whereas PPC<sub>STR</sub> neurons predominantly encode history bias. These distinctive patterns of neural encoding suggest that the CC transmits outcome history to the PPC, the PPC integrates this information to generate history bias and subsequently transmits this bias to the STR to influence history-dependent decision-making. Overall, our findings disclose the functional architecture of the posterior network that mediates an orderly cascade of information flow supporting history-dependent decision-making.

**Disclosures:** Y. Lee: None. S. Cinquemani: None. S. Korde: None. E. Hwang: None.

**Poster**

**PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.05/LL5

**Topic:** I.03. Decision Making

**Title:** A prefrontal to Amygdala pathway for adaptive sleep interruption

**Authors:** \*H. ZHU<sup>1</sup>, N. H. LAM<sup>2</sup>, J. SCOTT<sup>2</sup>, N. REDDER<sup>2</sup>, R. WIMMER<sup>1</sup>, M. A. PENZO<sup>3</sup>, M. HALASSA<sup>2</sup>;

<sup>1</sup>Tufts Univ. Sch. of Med., Boston, MA; <sup>2</sup>Tufts Univ., Boston, MA; <sup>3</sup>Natl. Inst. of Mental Hlth., Bethesda, MD

**Abstract:** Sleep is an evolutionarily conserved behavior with multiple functions such as energy homeostasis, toxic waste removal and memory consolidation. While significant progress has been made in understanding these functions, the mechanisms by which sleep is rapidly modulated in response to environmental contingencies remain poorly understood. Research on human subjects suggests both associative and contextual factors contributions to this decision-making process. Individuals are more likely to awaken when their name is called (an associative factor), and contextual elements, such as the difference between sleeping through fireworks on New Year's Eve versus being awakened by the same sound at other times, highlight the importance of context. Neuroimaging has identified the involvement of the prefrontal cortex (PFC) and amygdala in goal-directed sleep interruption, but the precise mechanisms remain elusive due to the challenges of probing these circuits in the human brain. Here, we aim to identify neural mechanisms that selectively couple sleep interruption to behaviorally relevant environmental signals, a process we term adaptive sleep interruption. We first developed two different adaptive sleep interruption paradigms in mice using aversive (active avoidance) or appetitive (reward) models. In both paradigms, mice showed increased arousal probability to a conditioned stimulus (CS+) during sleep—but only in the environment where the association was learned—indicating context- and cue-specific sleep interruption independent of emotional valence. Using advanced circuit dissection tools, we found that both amygdala and PFC are involved in this process. The amygdala showed enhanced encoding of task cues after conditioning. Intervention of different amygdala subdivisions selectively disrupted CS+/-, but not CS-/-induced sleep interruption. Furthermore, we investigated the role of the PFC in regulating the contextual component of sleep interruption. Mice showed preferential interruption to CS+ only in the conditioned environment, and PFC inactivation reinstated CS+/-induced interruption only in neutral contexts. Moreover, PFC neuronal activity showed context-specific shifts, with higher-dimensional coding observed in safety contexts. This suggests that the PFC may exert top-down control over learned associations, suppressing amygdala-mediated sleep interruption in neutral environments. Overall, by understanding how environmental cues influence sleep behavior at the neural level, we may uncover insights that could lead to novel therapeutic interventions for sleep-related disorders.

**Disclosures:** H. Zhu: None. N.H. Lam: None. J. Scott: None. N. Redder: None. R. Wimmer: None. M.A. Penzo: None. M. Halassa: None.

## **Poster**

### **PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.06/LL6

**Topic:** I.03. Decision Making

**Support:** Ministry of Science and Technology of China Grant 2022ZD0204900  
Local Science and Technology Development Fund  
YDZX20233100001002  
National Key R&D Program of China 2023YFA1009402

**Title:** Posterior parietal cortex mediates rarity-induced decision bias and learning under uncertainty

**Authors:** \*W. SHENG<sup>1</sup>, X. HUANG<sup>1</sup>, Y. XIE<sup>2</sup>, M. C. TSAKIRIS<sup>3</sup>, Y. YANG<sup>1</sup>;  
<sup>1</sup>Sch. of Life Sci. and Technol., ShanghaiTech Univ., Shanghai, China; <sup>2</sup>Lin Gang Lab., Shanghai, China; <sup>3</sup>Acad. of Mathematics and Systems Science, Chinese Acad. of Sci., Beijing, China

**Abstract:** Optimal decision-making under uncertainty is critical for survival, yet real-world decisions often deviate from optimality. Here, we report a rarity-induced bias in humans and mice, where rare events exert a stronger and more persistent impact on future decisions than common events. Optogenetic manipulations demonstrate two opposing roles of the posterior parietal cortex (PPC): generating rarity-induced bias throughout learning, and driving optimal choices in the expert stage. In vivo recordings support both roles: preceding rare rewards enhance the activity of PPC neurons encoding the biased choice while suppressing neurons encoding the opposite choice, causing the bias; learning enhances the stimulus-encoding capacity of PPC neurons, promoting optimal choices. Our study uncovers an evolutionarily conserved rarity impact in decision-making, and elucidates essential roles of PPC in mediating rarity-induced bias and learning under uncertainty.

**Disclosures:** W. Sheng: None. X. Huang: None. Y. Xie: None. M.C. Tsakiris: None. Y. Yang: None.

**Poster**

**PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.07/LL7

**Topic:** I.03. Decision Making

**Support:** Travis NIMH R01-MH085739

**Title:** Fixed Interval Training Reduces Impulsive Choice: A Causal Role for the Prefrontal-to-Dorsal Medial Striatum Circuit

**Authors:** \*M. J. MCLEOD<sup>1</sup>, S. BURKE<sup>2</sup>, E. STANFORTH<sup>2</sup>, J. MCCLOSKEY<sup>3</sup>, E. CHU<sup>2</sup>, C. MAHONEY<sup>6</sup>, R. SOUTHERN<sup>7</sup>, L. WEST<sup>7</sup>, K. PANFIL<sup>7</sup>, C. VONDER HAAR<sup>4</sup>, T. SMITH<sup>5</sup>;  
<sup>1</sup>Neurosci., Ohio State Univ., Sunbury, OH; <sup>2</sup>Ohio State Univ., Columbus, OH; <sup>3</sup>Neurosci., Ohio State Univ., COLUMBUS, OH; <sup>4</sup>Neurosci., Ohio State Univ., Columbus, OH; <sup>5</sup>Ohio State Univ.,

COLUMBUS, OH; <sup>6</sup>Neurosci., The Ohio State Univ., Columbus, OH; <sup>7</sup>Kansas State Univ., Manhattan, KS

**Abstract:** Impulsive choice refers to the preference for a smaller reward available sooner (SS, “impulsive”) over a larger reward available later (LL, “self-controlled”), under conditions where the larger reward provides the most amount of reward over time. Impulsive choice is associated with ADHD, substance use disorder, problem gambling, and several other maladaptive behaviors and psychiatric disorders. These conditions provide an impetus for researching the function and structure of the neural circuitry which produces impulsive choice, as well as interventions which reduce it. Fixed interval (FI) training is a behavioral intervention shown to increase LL choices and interval timing precision in rats, two functions associated with the prelimbic cortex (PL) and dorsal medial striatum (DMS) regions of the rodent brain. FI training may induce this improvement through plasticity changes in these regions. Thus, the purpose of the following experiments was to identify FI-induced plasticity changes in the PL and DMS and whether inhibition of these regions prevented training effects. Plasticity changes were assessed using diffusion tensor imaging (DTI), immunohistochemistry (IHC), and multiplex gene expression panels (NanoString). Functional significance was assessed with chemogenetic (Gi-DREADDs) methods. The DTI experiment revealed that training improved PL axonal organization and PL-DMS connectivity in self-controlled rats. The IHC and gene expression panels to assess synaptic plasticity changes showed that excitatory synapse protein (PSD-95) and several immediate early genes were upregulated in the FI group, along with downregulation of inhibitory receptors (SST). Inhibitory DREADDs to the PL cortex during FI training ablated the FI training effects and did not increase LL choices compared to controls. A follow-up experiment inhibited the PL to DMS circuit during the impulsive choice task and similarly produced increased impulsive choice. Overall, these data suggest a causal role of the PL and DMS in impulsive choice and selective plasticity changes in these regions accounting for intervention-mediated improvements in self-control.

**Disclosures:** M.J. McLeod: None. S. Burke: None. E. Stanforth: None. J. McCloskey: None. E. Chu: None. C. Mahoney: None. R. Southern: None. L. West: None. K. Panfil: None. C. Vonder Haar: None. T. Smith: None.

## **Poster**

### **PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.08/LL8

**Topic:** I.03. Decision Making

**Support:** ASPIRE Medical Research Program

**Title:** Mild sleep deprivation and shifting test time of day increased effortful choice on the effort discounting task.

**Authors:** \*F. AREGA, E. CHU, M. MCLEOD, J. FITZGERALD, D. AKBARZADEH, O. KOKIKO-COCHRAN, K. M. MARTENS, C. VONDER HAAR;  
The Ohio State Univ., Columbus, OH

**Abstract:** It is well recognized that getting sufficient and consistent sleep every night is important. Unfortunately, this is not achieved by many. The NIH recommends that adults receive 7-8 h of sleep each night but the prevalence of sleep deprivation is growing and is one of the leading reasons for sleep clinic visits. Many lifestyle factors like shift work, unhealthy sleep habits, and stress are reported causes of sleep deprivation. This in turn can lead to cognitive deficits in domains like sustained attention, memory, and motivation. Review of existing literature shows a lack of an effort-expenditure perspective on motivation following sleep deprivation. To bridge this gap, we looked at the effects of gentle handling sleep deprivation on performance on the Effort Discounting Task (EDT), an operant behavioral task that assesses motivation as a measure of effort expenditure. In this task, mice are presented with a high effort; high reward (HE/HR) or a low effort; low reward (LE/LR) choice. The effort requirement increases across blocks of trials within a session with later trials requiring more effort for the HE/HR option. Two experimental cohorts of 8 male and 8 female C57BL/6 mice each (total n=32) were tested on this task. We hypothesized that mice that underwent sleep deprivation would show less effort expenditure and thus decreased motivation. Contrary to our hypothesis, the first experimental cohort exhibited increased effort expenditure after sleep deprivation. The second cohort was included to explore these results further. Similar to the first cohort, the second cohort showed increased effort expenditure following sleep deprivation. Additional behavioral testing was performed to further determine the cause of these results. We found an effect of behavioral testing time on task performance which mimicked the results post-sleep deprivation.

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## **Poster**

### **PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.09/LL9

**Topic:** I.03. Decision Making

**Support:** NIH Grant

**Title:** Prior encoding of superior colliculus in decision-making

**Authors:** \*Y. M. HONG<sup>1</sup>, V. N. THAKUR<sup>2</sup>, M. A. BASSO<sup>3</sup>;  
<sup>2</sup>Psychology, <sup>3</sup>Neurobio. and Biophysics, <sup>1</sup>Univ. of Washington, Seattle, WA

**Abstract:** Decision-making involves accumulating external sensory evidence and transforming it into a choice of action. When uncertain about the sensory evidence, prior experience informs our

decisions. A midbrain structure, superior colliculus(SC), plays a causal role in perceptual decision-making, however little is known whether or how SC encodes prior information. Here, we explored how priors impact decision-making behavior of macaques and the neuronal correlates of the impact of priors in SC. We employed behavioral models and neural population dynamical models. Two trained rhesus macaques performed a two choice orientation discrimination task using Glass patterns. Each session consisted of two blocks, first with equal orientation prior probability and a second with unequal orientation prior probability favoring either left or right choices. To understand subjects' strategy and the effect of priors, we used Generalized Linear Model-Hidden Markov Model (GLM-HMM) to fit choices. The model revealed that monkeys perform the task primarily with two internal states: an unbiased state and a state biased towards the more frequent orientation. Transitions between these two states occur primarily after the second block starts. These internal states remain fairly stable for hundreds of trials throughout the session in NHPs, in contrast to mice that switch every tens of trials. Next, we investigated whether these internal states are encoded in SC. The initial single-neuron analysis showed heterogeneity in encoding of both sensory evidence and internal priors. To examine the population-level effects of priors on SC activity, we used demixed Principal Component Analysis (dPCA) to isolate independent encoding axes related to stimulus, choice, and prior information. Our analysis demonstrated that prior information is significantly ( $p < 0.01$  in permutation test) represented in the SC throughout the duration of the trial, even before the presentation of the targets and sensory stimulus. This suggests a potential role for SC in integrating prior expectations to prepare for and process upcoming sensory input. Further investigation into the temporal dynamics and interactions of encoding axes may provide deeper insights into the neural mechanisms underlying the integration of prior information with sensorimotor transformation.

**Disclosures:** Y.M. Hong: None. V.N. Thakur: None. M.A. Basso: None.

## **Poster**

### **PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.10/LL10

**Topic:** I.03. Decision Making

**Support:** NIH Grant UF1NS122040

**Title:** Visual Decision-Making in Mice Reveals Evidence Accumulation Strategies Similar to Primates

**Authors:** \*V. N. THAKUR<sup>1</sup>, M. A. BASSO<sup>2</sup>;

<sup>2</sup>Neurobio. and Biophysics, <sup>1</sup>Univ. of Washington, Seattle, WA

**Abstract:** Decision-making enables organisms to navigate complex environments by integrating sensory and other information to guide actions. Although mostly studies in nonhuman and

human primates, the available tools for mechanistic investigation of decision-making remain limited in models. In contrast, mice offer rich molecular and genetic tools for probing neural cell specific circuits. Mouse decision-making studies typically rely on auditory or olfactory modalities whereas, fewer studies use visual decision-making tasks - the gold standard in nonhuman primate and human research, limiting direct comparative studies across species. Here, we investigate how mice perform evidence-based visual perceptual decisions and whether they employ similar computational strategies to humans and monkeys using the same visual paradigm. Trained mice performed the random dot motion direction discrimination task (RDM), a well-established visual paradigm for studying perceptual decision-making in primates. Our task included a manipulation of within-trial evidence by presenting transient motion pulses at different times of the trial (early, middle, and late). We found that the effect of motion pulses at different times during stimulus viewing biased choices more strongly when pulses appear earlier in the trial compared to later in the trial (slope coefficient -0.0612;  $z = -5.185$ ,  $p < 0.001$ ). Data obtained from 234 sessions across 10 mice showing this primacy effect, revealed that mice perform the RDM task by accumulating noisy visual evidence rather than taking a snapshot of instantaneous evidence to guide their choices. The accumulation of evidence appears to be a bounded process like nonhuman primates and humans, suggesting conserved computational principles govern visual decision-making across species. These findings establish mice as powerful and complementary model to primates for understanding how the brain forms visual evidence-based decisions. Our training methods demonstrate that mice can perform sophisticated visual perceptual decision-making tasks previously thought limited to primates, opening new avenues for investigating neural circuits underlying visual decision making and how these processes may be shared or specialized across mammalian species. References (PMID): 18354005, 30154467, 29779878, 30322902

**Disclosures:** V.N. Thakur: None. M.A. Basso: None.

## **Poster**

### **PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.11/LL11

**Topic:** I.03. Decision Making

**Support:** NSF/CAREER (#2235858)  
NIH/NIDA (#R01DA058653)

**Title:** Ghrelin selectively enhances the striosomal circuit to modulate decision- making

**Authors:** \*N. REYES<sup>1</sup>, A. A. SALCIDO<sup>1</sup>, A. FRIEDMAN<sup>2</sup>;

<sup>1</sup>Univ. of Texas at El Paso, El Paso, TX; <sup>2</sup>Biol. Sci., UTEP, El Paso, TX

**Abstract:** The bidirectional relationship between the gut and brain, known as the gut-brain axis (GBA), regulates both physiological and cognitive states via hormones and neuropeptides.

Disruptions in this axis have been implicated in neuropsychiatric disorders such as SUD, PTSD, suicidality (stress disorders), and Huntington's disease. These conditions often show elevated levels of the hunger hormone ghrelin and hyperactivity in the striosomal compartment of the striatum, a brain region involved in decision-making. While both are dysregulated amongst these disorders, the possibility of a direct functional relationship between the two remains relatively unexplored and prompted for further investigation. We hypothesized that ghrelin selectively enhances activity in striosomes, but not the matrix, leading to altered decision-making through circuit-specific modulation. To test this, we administered ibutamoren mesylate (IBU; 1 mg/kg IP), a ghrelin receptor agonist, to Long Evans rats. Brains were processed using immunohistochemistry (IHC) to quantify cFos expression, a marker of neuronal activity, across 50 regions. We observed significantly increased cFos expression in striosomes but not matrix. Whole-brain analysis showed widespread activation of the striosomal circuit, including areas involved in decision-making. To further investigate, we used an OPRM1-Cre rat model and administered IBU at varying doses (1x, 2x, and saline). Brain tissue was stained for cFos, phosphorylated pyruvate dehydrogenase (pPDH, an inactivity marker), and growth hormone secretagogue receptor (GHSR). Analysis revealed GHSR expression was denser in striosomes than matrix. A biotinylated ghrelin binding assay also revealed greater ghrelin binding in dorsomedial (DMS) compared to dorsolateral (DLS) striatum. We also observed increased cFos in DMS at both doses, while pPDH was elevated in DLS, suggesting an inverse activation pattern. These results highlight ghrelin's selective engagement of the striosomal decision-making circuit and provide insights into the interaction between metabolic signals and cognitive function, suggesting therapeutic potential for targeting the GBA in related disorders. See linked poster titled "Causal Role of Striosomes in Ghrelin-Induced Shifts in Conflict and Novelty-Driven Decision-Making"

**Disclosures:** N. Reyes: None. A.A. Salcido: None. A. Friedman: None.

## **Poster**

### **PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.12/LL12

**Topic:** I.03. Decision Making

**Support:** NSF CAREER (#2235858)  
NIH/NIDA R01DA058653  
G-RISE T32GM144919 / R25GM132959-05

**Title:** Causal role of striosomes in ghrelin-induced shifts in conflict and novelty-driven decision making

**Authors:** \*A. A. SALCIDO<sup>1</sup>, N. F. REYES<sup>2</sup>, A. FRIEDMAN<sup>3</sup>;

<sup>1</sup>Biol., <sup>2</sup>biology, Univ. of Texas at El Paso, El Paso, TX; <sup>3</sup>Biological Science, UTEP, El Paso, TX



**Abstract:** Decision-making (DM) is a core cognitive process disrupted across disorders such as substance use disorder, PTSD, suicide, and Huntington's disease. Many of these conditions involve dysregulated ghrelin signaling and increased striosomal activity in the striatum, suggesting a shared mechanism. The brain-gut axis is known to influence motivation, but how it shapes DM remains unclear. We first examined neural activation after administering Ibutamoren Mesylate (IBU), a ghrelin receptor agonist, to adult Oprm1-Cre rats (n = 30). cFos expression was elevated in the dorsomedial striatum (DMS), while phosphorylated pyruvate dehydrogenase (pPDH), a marker of reduced activity, was higher in the dorsolateral striatum (DLS; p = 0.0146). This suggests a functional DMS-DLS seesaw, with DMS as the primary target of ghrelin's effects. To understand how this activation pattern influenced behavior, we turned to our previously developed striosomal model, which predicted that ghrelin would alter performance in tasks involving conflict or novelty. When injected with IBU (1 mg/kg), rats showed no behavioral changes in simple tasks. However, in high-demand tasks, IBU increased novelty-seeking, social dominance, and preference for moderately novel stimuli. To test causality, we used Oprm1-Cre rats (n = 30) to target the DMS with Cre-dependent DREADDs (hM4D(Gi), hM3D(Gq)) in a validated model with >75% striosomal specificity. Two groups were injected: one to inhibit and one to excite striosomes. Rats were tested across six behavioral tasks. Inhibiting striosomes reversed IBU-induced behaviors, while exciting striosomes mimicked IBU's effects in the absence of hormone. These effects were specific to conflict-based decision-making. Together, these findings identify DMS striosomes as a key target of ghrelin signaling and reveal a compartmentalized mechanism by which internal states, shaped by hormones like ghrelin, modulate neural circuits to guide behavior.

**Disclosures:** A.A. Salcido: None. N.F. Reyes: None. A. Friedman: None.

## **Poster**

### **PSTR241: Neural Mechanisms: Maladaptive Choice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR241.13/LL13

**Topic:** I.03. Decision Making

**Title:** Information-geometric foundations of non-rational choices in the human brain and Large Language Models

**Authors:** \*Y. TAMORI<sup>1</sup>, A. ONZO<sup>2</sup>, S. NOZAWA<sup>3</sup>, K. MOGI<sup>4</sup>;

<sup>1</sup>Grad. Sch. of Arts and Sci., The Univ. of Tokyo, Meguro-ku, Japan; <sup>2</sup>The Univ. of Tokyo, Hadano-Shi, Japan; <sup>3</sup>Dept. of Gen. Systems Studies, The Univ. of Tokyo, Grad. Sch. of Arts and Sci., Meguro, Japan; <sup>4</sup>Sony Computer Sci. Labs., Shinagawa-Ku, Japan

**Abstract:** In decision-making processes, the human brain often deviates from the optimal solution. This phenomenon is well-documented in prospect theory (Kahneman & Tversky, 1979), illustrating humans' tendency to prefer risk-averse choices over rationality. Similarly, large language models (LLMs), despite being trained to minimize loss functions, are known to

exhibit behaviors that deviate from rationality (Mirzadeh et al., 2024; Wei et al., 2022). Such non-optimal decisions seem inconsistent with the principle of survival of the fittest, raising critical questions about the underlying computational mechanisms. This study investigates these phenomena through an information geometric analysis. Our results reveal key concepts in decision-making theory—such as utility functions (von Neumann & Morgenstern, 1944) and the Weber-Fechner law for sensory evaluation (Weber, 1834; Fechner, 1860)—naturally emerge as intrinsic dynamics of neural circuits. Moreover, although it is known that the e-connection in information geometry describes learning dynamics in neural networks (Amari, 2001, 2016), our analysis further demonstrates that the m-connection governs AI-alignment dynamics within neural networks. Furthermore, we formally embed the transformer algorithm, which underpins LLMs, into this information geometric framework, demonstrating its theoretical consistency. We also propose that the behavioral modulation caused by differences between risk-averse and profit-seeking motivations in gambling scenarios can be effectively analyzed and simulated using this geometric framework. By mathematically clarifying algorithms and statistical quantities, we anticipate that information geometry will become a central analytical tool in computational neuroeconomics (Glimcher & Rustichini, 2004). Building on these theoretical insights, we experimentally and mathematically compare choice behaviors among humans, LLMs, and theoretical models when faced with gambles that have identical expected values but different contents. Our results provide deeper understanding of the cognitive mechanisms supporting irrational decision-making and suggest that information geometry holds potential as a foundational approach in this interdisciplinary field.

**Disclosures:** Y. Tamori: None. A. Onzo: None. S. Nozawa: None. K. Mogi: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.01/LL14

**Topic:** I.04. Executive Functions

**Title:** Effect of video game practice on response inhibition in emotional contexts

**Authors:** \*L. LLAMAS-ALONSO<sup>1</sup>, V. HUERTA<sup>2</sup>;

<sup>1</sup>Psychology, Univ. Autónoma de Baja California, Ensenada, Mexico; <sup>2</sup>Inst. de Neurociencias, Univ. de Guadalajara, Guadalajara, Mexico

**Abstract:** Action video games demand rapid responses and offer immediate reward feedback that activates the mesolimbic-cortical dopaminergic circuit and induces frontostriatal plasticity. Moreover, they unfold within an ecosystem of continuous feedback and social competition, saturated with both pleasant and unpleasant emotional cues. Understanding how this combination of reinforcing stimulation and affective valence impacts behavioral regulation is crucial given the growing concerns about impulsive control and players' socioemotional health. The aim of this study was to determine whether

habitual action video game practice affects inhibitory control (IC) when task-irrelevant information carries emotional valence. Thirty action video game players (VGP;  $\geq 7$  h/week) and 31 non-players (CG) completed a Go/NoGo task featuring background images with neutral, pleasant, and unpleasant valence. Reaction times and percentages of Go hits and correct inhibitions (IC) were recorded. A mixed ANOVA (group  $\times$  valence) included weekly gaming hours as a covariate. For IC, weekly gaming hours did not explain additional variance, nor was there a main effect of group. However, a significant group  $\times$  valence interaction emerged ( $F = 3.50, p = .03, \eta^2 = .06$ ). VGPs exhibited higher IC than CGs only in response to unpleasant stimuli ( $\Delta \approx +13\%$ ), with no differences observed for neutral or pleasant valences. Reaction times showed no differences, ruling out a speed-accuracy trade-off. Experience with action video games appears to fine-tune frontocingulate inhibitory circuits specifically when the task requires suppressing responses to aversive cues, suggesting an affect-specific, rather than generalized, transfer effect. These findings support the responsible use of video games as a potential tool to strengthen inhibitory control in populations with emotional dysregulation. Future studies should manipulate gaming dosage and incorporate neurophysiological measures to identify the neural mechanisms associated with prolonged video game exposure.

**Disclosures:** L. Llamas-Alonso: None. V. Huerta: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.02/LL15

**Topic:** I.04. Executive Functions

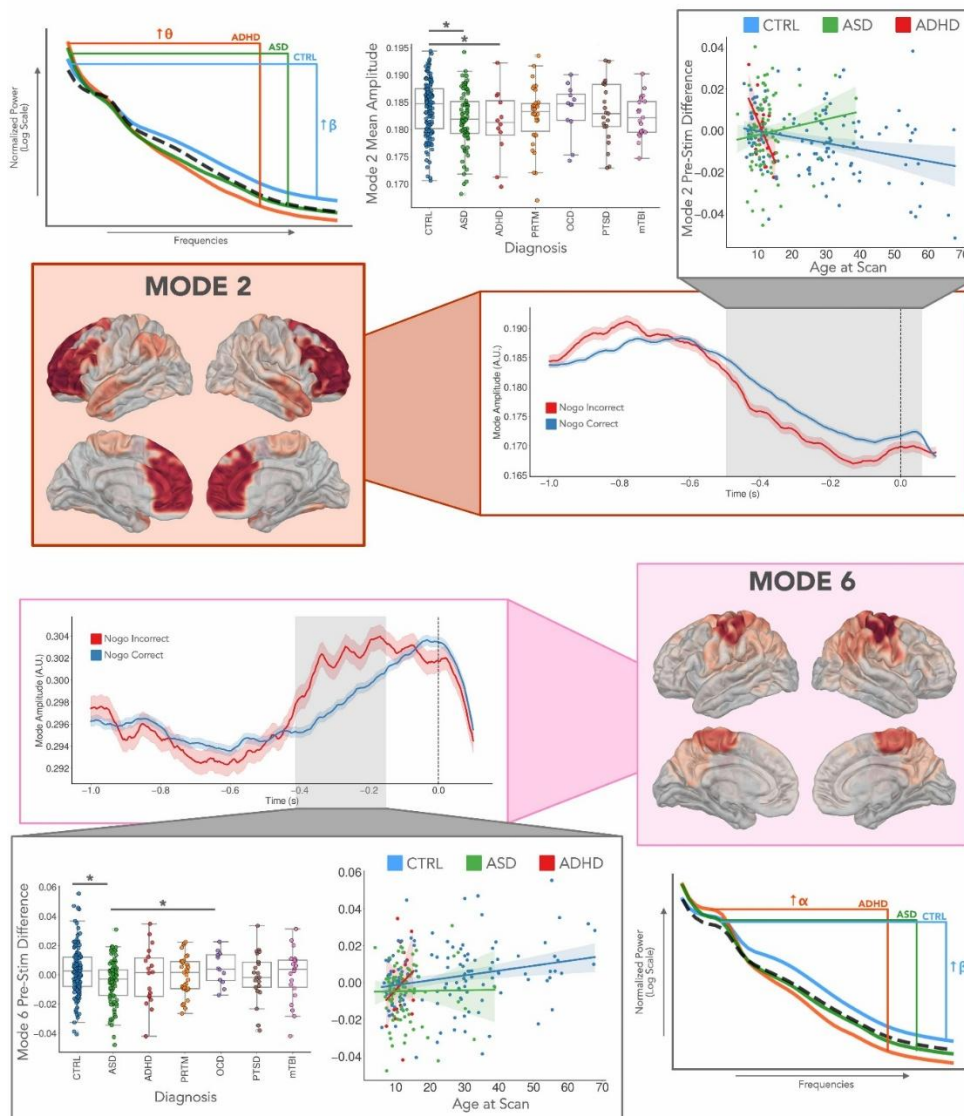
**Title:** Frontal network dynamics predict impulsive behaviour across a transdiagnostic cohort

**Authors:** \*K. MITHANI<sup>1,3</sup>, S. COLEMAN<sup>4</sup>, E. ANAGNOSTOU<sup>2</sup>, M. J. TAYLOR<sup>3</sup>, G. M. IBRAHIM<sup>1,3</sup>;

<sup>1</sup>Inst. of Biomed. Engin., <sup>2</sup>Pediatrics, Univ. of Toronto, Toronto, ON, Canada; <sup>3</sup>Neurosciences & Mental Hlth., The Hosp. For Sick Children, Toronto, ON, Canada; <sup>4</sup>Neurosciences & Mental Hlth., Hosp. for Sick Children, Toronto, ON, Canada

**Abstract:** The ability to maintain inhibitory control is a fundamental aspect of cognition, disruptions in which contribute to various neuropsychiatric diseases. However, the network dynamics that support inhibitory control remain poorly understood. In this study, we examined network dynamics in a diverse population across the lifespan as they completed a cognitive task probing inhibitory control. We analyzed behavioural and magnetoencephalography data from 375 individuals aged 4-68 (median 14.7), including 152 healthy controls and 223 with neuropsychological diagnoses, during a Go/Nogo task. This included participants with autism spectrum disorder (ASD, n=90) and attention-deficit/hyperactivity disorder (ADHD, n=18). Incorrect Nogo responses indexed lapses in inhibitory control, whereas incorrect Go responses indicated lapses in attention. After pre-processing and source localization, we applied data-

driven, self-supervised dynamic network modes analysis to identify six spatially, spectrally, and temporally resolved brain states. Two modes—a frontal theta network and a sensorimotor beta network—exhibited group-level differences preceding inhibitory but not attentional lapses during the interstimulus interval (permuted  $p < 0.010$ ). Specifically, reduced frontal theta activity (reflecting impaired top-down control) and increased sensorimotor beta activity (reflecting premature motor planning) both preceded impulsive behaviour. The magnitude of these deviations followed a neurodevelopmental trajectory with age ( $p = 0.018$ ), disrupted in ASD and accelerated in ADHD. Individuals with neurodevelopmental conditions also spent significantly less time in the frontal theta mode during the task compared to controls ( $p = 0.022$ ). These findings from a large, transdiagnostic cohort show that reduced frontal theta activity increases susceptibility to lapses in inhibitory control, shaping behaviour even before stimulus onset. These results may inform targeted neurotherapeutic interventions for neuropsychiatric disorders marked by impaired impulse control.



**Disclosures:** K. Mithani: None. S. Coleman: None. E. anagnostou: None. M.J. Taylor: None. G.M. Ibrahim: D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); LivaNova Inc.. F. Consulting Fees (e.g., advisory boards); LivaNova Inc., Synergia Inc., Medtronic Inc..

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.03/Web Only

**Topic:** I.04. Executive Functions

**Title:** Relationship between attention and inhibition to emotional expressions in adolescents: an electrophysiological study

**Authors:** \*A. ARVIZU-OVIEDO<sup>1</sup>, V. HUERTA<sup>2</sup>, J. RAMOS-LOYO<sup>2</sup>, L. LLAMAS-ALONSO<sup>1</sup>;

<sup>1</sup>Facultad de Ciencias Administrativas y Sociales, Univ. Autónoma de Baja California, Ensenada, Mexico; <sup>2</sup>Inst. de Neurociencias, Univ. de Guadalajara, Guadalajara, Mexico

**Abstract:** During adolescence, uneven development between mature subcortical limbic regions—linked to high emotional reactivity—and still maturing prefrontal regions—responsible for cognitive control—affects impulse and emotion regulation. Selective attention and response inhibition are key for self-control and emotional regulation: attention prioritizes relevant information and filters distractions, while inhibition suppresses inappropriate responses. Though these processes have independent neural bases, they remain closely related. This study examined whether greater attentional capacity predicts better inhibitory control to emotional facial expressions, using behavioral and electrophysiological measures. Emotional expressions were also analyzed across tasks to assess their impact on performance. Forty-four adolescents performed Oddball (attention) and Go/No-Go (inhibition) tasks with sex recognition (control), happiness, and anger conditions. EEG recorded the P300 component at Fz, Cz, and Pz. Behavioral results showed significant accuracy differences for low-probability trials: Oddball ( $F(2,86) = 26.55, p < .001, \eta^2 = .38$ ), Go/No-Go ( $F(2,86) = 9.17, p < .001, \eta^2 = .17$ ). Accuracy was lower for anger than sex and happiness in Oddball ( $p < .001$ ). In Go/No-Go, inhibition accuracy was higher for sex than happiness ( $p = .05$ ) and anger ( $p < .001$ ). Reaction times also differed: Oddball ( $F(2,86) = 174.92, p < .001, \eta^2 = .80$ ), Go/No-Go ( $F(2,86) = 88.31, p < .001, \eta^2 = .67$ ), with faster responses in the sex condition. Oddball accuracy predicted Go/No-Go inhibition accuracy (sex  $R^2 = .13, p = .009$ ; happiness  $R^2 = .17, p = .003$ ; anger  $R^2 = .10, p = .02$ ). No P3 amplitude differences appeared between conditions in Oddball Target trials. In Go/No-Go No-Go trials, P3 was higher for sex than anger ( $p = .003$ ), with a trend for happiness ( $p = .07$ ). P3 in Oddball predicted P3 in Go/No-Go at Cz (sex  $R^2 = .27, p < .001$ ; happiness  $R^2 = .11, p = .01$ ; anger  $R^2 = .09, p = .02$ ), at Fz for happiness ( $R^2 = .07, p = .04$ ) and anger ( $R^2 = .13, p = .01$ ), and at Pz only for sex ( $R^2 = .26, p < .001$ ). No correlations were found between P3 and behavior. These findings show that emotional expressions—especially anger—disrupt attention

and inhibition in adolescents, as reflected by lower accuracy and slower responses. Greater P3 amplitude to neutral stimuli suggests lower cognitive demand than emotional ones. The predictive link between attention and inhibition, along with cross-task P3 correlations, suggests shared neural mechanisms and interconnected development. Overall, results highlight the emotional context's influence on cognitive control and how attentional control aids emotional regulation.

**Disclosures:** A. Arvizu-Oviedo: None. V. Huerta: None. J. Ramos-Loyo: None. L. Llamas-Alonso: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.04/LL16

**Topic:** I.04. Executive Functions

**Title:** Motor Clocks, Broken Brakes and The Ticking Brain: How Movement Speed Forecasts Cognitive Exhaustion in Parkinson's Disease

**Authors:** \*H. SINGH;

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**Abstract:** Parkinson's disease (PD) is distinguished by progressive motor and cognitive decline. While the role of cognition contributing to movement impairment have been widely explored, the opposite of how these motor symptoms may forecast cognitive control breakdown remains under-investigated. This study explores how motor timings, assessed through reaction timings in the Finger Tapping Test (FTT), can predict failures in inhibitory control during a stop-signal task (SST) in individuals with PD.

Ninety-two individuals with idiopathic PD (Hoehn & Yahr stages I-III) were included in this study from real-world movement disorders outpatient settings during stable functional states. All subjects completed the FTT followed by a two-block SST involving pass and stop trials.

Regression analysis was run to see how motor timings predict SST accuracy and Friedman's two-way ANOVA were used to evaluate inhibitory control performance across blocks.

Results showed that slower FTT reaction times significantly predicted poorer SST accuracy (Multiple R = 0.607,  $R^2 = 36.8\%$ ,  $p < 0.001$ ). Particularly, pass trials showed higher error rates than stop trials (Pass-ER:  $0.915 \pm 0.100$ ; Stop-ER:  $0.565 \pm 0.243$ ), despite faster responses (Pass-RT:  $641.3 \pm 91.54$  ms; Stop-RT:  $575.43 \pm 119.26$  ms,  $p < 0.001$ ). Moreover, stop error rates significantly worsened across blocks, revealing a progressive collapse and decline in inhibitory control under sustained cognitive demand.

The findings from the result suggest that impaired movement timing contemplates deeper dysfunction in cortico-basal-ganglia-thalamo-cortical circuitry, especially within the SMA, STN, and prefrontal cortex, disrupting both temporal cueing and inhibition. This predictive power of motor speed may provide a scalable, low-cost biomarker to anticipate cognitive decline

trajectories in PD. This opens the door to timing-based screening and rehabilitation strategies that intervene before executive exhaustion starts to drain cognitive capacity.

By reframing movement as a forward signal, rather than a downstream consequence which has been generally regarded as the cause of cognitive breakdown, this study offers changing insights in understanding the motor-cognitive loop in PD.

**Disclosures:** H. Singh: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.05/LL17

**Topic:** I.04. Executive Functions

**Support:** NSF GRFP

**Title:** Neural Decoding of Successful Action Cancellation in Human Local Field Potentials

**Authors:** \*M. E. ALARIE<sup>1</sup>, W. F. ASAAD<sup>2</sup>;

<sup>1</sup>Inst. for Biology, Engineering, and Med., <sup>2</sup>Neurosurg., Brown Univ., Providence, RI

**Abstract:** The stop signal task (SST) is the gold standard paradigm for studying response inhibition, or the ability to halt ongoing actions. In traditional SST designs, participants are instructed to respond to a go signal or, on ~30% of the trials, withhold their response when a delayed stop signal appears following the go signal. Studies have observed clear response inhibition deficits across various neurological disorders, demonstrated by longer stop-signal reaction times compared to healthy controls. Converging evidence has identified a “stopping network,” including the pre-supplementary motor area (pre-SMA), inferior frontal gyrus (IFG), and subthalamic nucleus (STN), as key nodes supporting action cancellation. However, the precise neural dynamics predictive of successful versus failed response inhibition remain incompletely understood, particularly in regions outside the canonical stopping network. This is especially relevant in the case of psychiatric disorders, where deficits of action cancellation often occur in the absence of overt motor dysfunction. In this study, we aimed to delineate the neural regions predictive of successful versus failed action stopping in 3 patients undergoing intracranial monitoring for intractable epilepsy. To assess the role of spectral power in predicting successful versus failed action cancellations, sliding receiver operating characteristics (ROCs) were calculated by trial at the time of go and stop cue onset, respectively. We observed that theta (AUC ~0.67,  $p < 0.05$ ) and low gamma (AUC ~0.67,  $p < 0.05$ ) power of the thalamus following the stop cue as well as alpha power of the anterior cingulate cortex preceding the stop cue were predictive of stop trial success (AUC ~0.64,  $p < 0.05$ ). Further, high gamma power of the anterior cingulate following the go cue was predictive of stop trial success (AUC ~0.67,  $p < 0.05$ ). Results from this study suggest that there are regions predictive of response inhibition beyond those implicated in the stopping network.

**Disclosures:** M.E. Alarie: None. W.F. Asaad: None.

**Poster**

**PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.06/LL18

**Topic:** I.04. Executive Functions

**Support:** NIH Grant 1R01NS134772-01  
Renée James Seed Grant to Initiative to Accelerate Scientific Research  
NINDS Grant F31NS132549

**Title:** Stereo EEG reveals distinct temporal signatures during a novel continuous movement stop task

**Authors:** K. SCHULTZ<sup>1</sup>, \*S. PARMIGIANI<sup>1</sup>, A. ROCKHILL<sup>2</sup>, A. RASLAN<sup>3</sup>, N. C. SWANN<sup>1</sup>;

<sup>1</sup>Univ. of Oregon, Eugene, OR; <sup>2</sup>Neurolog. Surgery, Oregon Hlth. & Sci. Univ., Eugene, OR;

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**Abstract:** Inhibitory control, the critical ability to suppress unwanted thoughts and actions, is fundamental for daily life, yet its precise neural underpinnings are still debated. A key limitation of traditional investigatory paradigms, such as the stop-signal task (SST), is their inherent temporal ambiguity and inefficient sampling of stop trials, which complicates efforts to accurately identify neural correlates of specific inhibitory components. We used a novel Continuous Movement Stop Task (CMST) to overcome this while recording stereoelectroencephalography (SEEG). We investigated beta (13- 30Hz) and theta (4- 7Hz) oscillations in SEEG. The CMST allows direct observation of movement termination since it requires continuous movement and stopping in response to planned or unplanned cues. Twelve patients implanted for surgical evaluation of medically intractable epilepsy performed the CMST task while SEEG was recorded. Participants stopped faster on planned trials compared to unplanned ( $p=.033$ ), but stop completion times (SCT) were more variable for planned stopping ( $p=.025$ ). Of 832 analyzed SEEG channels, 89.2% had statistically significant differences during task events. Electrophysiological analysis revealed varied channel engagement by frequency and task condition. For beta oscillations during the appearance of the stop signal, 5.2% of channels responded exclusively to planned trials, 10.9% to unplanned trials, 7.2% responded to both planned and unplanned stop trials, and 5.3% to the condition difference. For beta activity related to stop completion, they were 4.4% (planned), 12.3% (unplanned), 5.5% (both planned and unplanned), and 5.4% (difference). In the theta band targeting the stop signal presentation, 6.5% of channels responded exclusively to planned trials, 11.5% exclusively to unplanned trials, 8.8% to both, and 10.2% solely to the difference. For theta activity at stop completion, these were 7.7% (planned), 11.9% (unplanned), 9.6% both, and 10.8% (difference). Our study, combining CMST with SEEG, highlights distinct patterns of theta and beta oscillatory engagement in



inhibitory control, influenced by stop predictability. Both frequency bands showed a higher proportion of exclusively responsive channels during unplanned stops than during planned stops, during the stop signal, and movement termination phases. This provides valuable information about the complex interplay of neural oscillations underlying stopping behavior. Future analyses will focus on the detailed temporal characteristics and specific functional contributions of oscillatory activities to clarify their roles in motor inhibition.

**Disclosures:** K. Schultz: None. S. Parmigiani: None. A. Rockhill: None. A. Raslan: None. N.C. Swann: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.07/LL19

**Topic:** I.04. Executive Functions

**Support:** NIH R01 HD098097

**Title:** Cumulative Impacts of Smartphone Use on Cognitive Control and Human Brain White Matter Connectivity

**Authors:** \*L. HU<sup>1</sup>, D. ZWEBEN<sup>2</sup>, J. M. CHEIN<sup>1</sup>;  
<sup>1</sup>Psychology, <sup>2</sup>Temple Univ., Philadelphia, PA

**Abstract:** In the era of intelligent technology, smartphones not only serve as tools for convenience, but also likely influence cognition and behavior over time. While prior research has linked excessive smartphone use to decreased cognitive control, most studies rely on short-term usage metrics, neglecting the cumulative effects of long-term smartphone use on cognitive control and brain structure. This gap is addressed by examining how both recent and prolonged smartphone use impact cognitive control and white matter connectivity. We recruited 434 participants (167 females) with ages ranging from 7 to 21 years, and used a multi-method assessment of smartphone use, including self-report (Mobile Technology Engagement Scale; MTES), objective (recent smartphone usage metrics based on weekly average screen time and checking frequency), and long-term history of use (number of years since first smartphone ownership). Cognitive control was assessed through a Flanker task, and Automated Fiber Quantification of diffusion weighted images (DWI) examined white matter microstructure in the adult (18-21) subsample, who varied considerably in years of smartphone use. Results revealed that the Flanker effect decreased with age, reflecting improved inhibitory control, but this relationship was moderated by long-term usage duration ( $b = 0.013$ ,  $t = 2.849$ ,  $p = 0.005$ ) and MTES score ( $b = 0.027$ ,  $t = 2.194$ ,  $p = 0.029$ ). White matter connectivity analysis further demonstrated that only long-term usage duration significantly correlated with fractional anisotropy in key white matter tracts, including the anterior frontal and orbital regions of the corpus callosum, the left cingulum cingulate tract, and the right anterior thalamic radiation.

These results suggest that smartphone use not only impacts cognitive control behaviorally, but may alter the white matter connectivity structure of the human brain. The dissociation between long-term and recent usage metrics underscores the importance of longitudinal assessments in digital behavior research. While the temporal directionality of observed correlations remains unclear, these findings highlight potential neurodevelopmental consequences of early and sustained smartphone exposure.

**Disclosures:** **L. Hu:** None. **D. Zweben:** A. Employment/Salary (full or part-time): Temple University. **J.M. Chein:** None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.08/LL20

**Topic:** I.04. Executive Functions

**Support:** NSF 2342319

**Title:** Probing the temporal dynamics of the neural representations underlying conflict resolution

**Authors:** \***J. SELLERS**<sup>1</sup>, J. A. BRISSENDEN<sup>2</sup>, H. ZHANG<sup>2</sup>, J. JONIDES<sup>3</sup>, T. G. LEE<sup>4</sup>;  
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**Abstract:** Cognitive control refers to the collection of processes that allow us to engage in goal-directed behavior when our automatic impulses and habits conflict with our goals. Classic tasks used to study the conflict resolution process put task-irrelevant information into conflict with task-relevant information. For example, in the arrow Simon task, participants are instructed to respond to the direction of an arrow (left or right). The location of this arrow can either be incongruent or congruent to its direction, allowing researchers to test for differences in behavior and neural activity when conflict is present or not. Neurocomputational models of cognitive control have ascribed distinct functional roles to brain regions, such as the dorsolateral prefrontal cortex and anterior cingulate cortex, within larger cognitive control networks. Virtually all of this research has relied on tasks using free response times (RTs) as the primary dependent measure. However, free RT tasks have been shown to be susceptible to time-on-task confound for fMRI studies. Incongruent trials typically have longer RTs than congruent trials, and the activity of many task-relevant brain areas scale with RT. This has left it unclear if contrasts between incongruent and congruent trials reflect a genuine differential engagement of neural processes, presenting a challenge for investigating the neural mechanisms of conflict resolution. To explicitly address the time-on-task confound and to more directly probe the time course of conflict resolution processes, we used a forced-response version of the Simon task during fMRI scanning. The forced-response method involves fixing RT and varying stimulus onset, allowing

experimental control over processing time (PT). Participants performed the task with three stimulus onset times: a time when habitual information is present but goal-directed information is not (short PT), an intermediate time when goal-directed processing is beginning to override habitual information (medium PT), and a time when goal-directed processing should have overridden habitual processing (long PT). Our analyses revealed increased activity in cognitive control areas during conflict resolution that dissipated at longer PTs. Furthermore, we use model-based representation similarity analysis (RSA) to characterize the representations underlying the conflict resolution process in these regions. These results demonstrate that the forced-response method can be used to directly control for time-on-task confounds and highlight the time dependent nature of conflict resolution processes.

**Disclosures:** J. Sellers: None. J.A. Brissenden: None. H. Zhang: None. J. Jonides: None. T.G. Lee: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.09/LL21

**Topic:** I.04. Executive Functions

**Support:** VA Grant IK2CX001887

**Title:** Computational Evidence that Methylphenidate Improves Real-Time Inhibitory Control in Posttraumatic Stress Disorder

**Authors:** V. R. VASQUEZ, \*J. R. HOWLETT;  
VA San Diego Healthcare Syst., La Jolla, CA

**Abstract:** Deficient inhibitory control has been implicated in posttraumatic stress disorder (PTSD), and recent evidence suggests that this deficit may be reliably measured using a real-time sensorimotor control paradigm. The stimulant methylphenidate (MPH) is known to improve inhibitory control in attention-deficit hyperactivity disorder, and a small clinical trial found evidence that it may be effective for PTSD. This study tested the hypothesis that a single dose of MPH improves real-time inhibitory control in Veterans with PTSD. 17 Veterans with PTSD received a single dose of MPH 40 mg and placebo in a randomized, double-blind, crossover design. Participants completed the rapid assessment of motor processing (RAMP) task, a real-time motor control task in which they used a joystick to drive and stop a virtual car. We used a computational proportion-derivative (PD) control model to measure two parameters:  $K_p$ , a dynamic activation parameter, and  $K_d$ , a dynamic inhibition parameter. A linear mixed effects (LME) model was used to examine the influence of MPH on model parameters. One participant was excluded from analysis due to poor model fit and outlier parameter values. MPH had no significant effect on dynamic activation but was associated with significantly higher dynamic inhibition, controlling for dynamic activation ( $p < .03$ ). Session order had no significant effect on

model parameters, suggesting that RAMP parameters may represent robust, repeatable measures of control processing in clinical populations. In combination with previous research finding that PTSD is associated with impairments in real-time inhibitory control as measured by the RAMP paradigm, the current results suggest that a single dose of MPH may help correct this deficit. Computational indices of motor control may represent sensitive mechanistic measures of dysfunction in PTSD and its response to interventions.

**Disclosures:** V.R. Vasquez: None. J.R. Howlett: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.10/LL22

**Topic:** I.04. Executive Functions

**Title:** Attentional control processing traced by mismatch negativity and mismatch oscillatory response

**Authors:** \*Y. HORINAKA<sup>1</sup>, T. URAKAWA<sup>2</sup>, T. TERUNUMA<sup>1</sup>, K. TAKAHASHI<sup>1</sup>, S. ATARASHI<sup>1</sup>, T. KAMBARA<sup>1</sup>, O. ARAKI<sup>1</sup>;

<sup>1</sup>Tokyo Univ. of Sci., Tokyo, Japan; <sup>2</sup>Mazda Motor Corp., Hiroshima, Japan

**Abstract:** According to the Attentional Control Theory, when a behavioral task becomes attentionally demanding, individuals with high trait anxiety are susceptible to a sensory distraction (Eysenck et al., 2007). Such susceptibility is suggested to originate from degraded inhibition of the distraction. However, it remains unclear at which stage of sensory processing the degraded inhibition process in anxiety-prone individuals begins to occur following the onset of the sensory distraction. To clarify this issue, the present study attempted to test a hypothesis that mismatch negativity (MMN), an early event-related potential evoked by a deviant stimulus, would increase and mismatch oscillatory response (MOR) in the alpha band, an index of sensory suppression, would decrease for anxiety-prone individuals when the behavioral task is attentionally demanding. Participants performed the N-back tasks (N=1, 2, and 3) while task-irrelevant auditory stimuli (Task-irrelevant stimuli consisted of 1300 Hz and 1000 Hz tones.) were presented under an oddball paradigm. A total of 23 participants took part in the study (mean age = 24.3 years, SD = 7.48). The results of a two-way repeated measures analysis of variance for behavioral measures showed a decrease in accuracy ( $F(1.182, 23.633) = 32.25, p < 0.01$ ) and an increase in RT ( $F(2, 40) = 49.982, p < 0.01$ ) as the task difficulty increased. Results showed that MMN's enhancements, which occurred in the 3-back over the 1-back task at the latency of 100-200 ms, significantly correlated with an increase in STAI-T score across participants ( $r = 0.8266, p < 0.01$ ). This indicates that the degraded inhibition for anxiety-prone individuals begins to occur at such an early stage of sensory processing. In accordance with this, a decrease in MOR-alpha's power at the latency of around 100-300 ms, which occurred in the 2-back over the 1-back task, was significantly associated with an increase of STAI-T score ( $r = -$

0.5218,  $p < 0.05$ ), supporting that sensory suppression at early sensory processing weakened in anxiety-prone individuals. The results suggested that participants with higher trait anxiety had more difficulty in inhibiting attention to distractors, where the susceptibility was reflected in enhanced MMN amplitudes and the suppression was reflected in reduced MOR power. These findings shed light on the temporal profile of inhibition processing for anxiety-prone individuals.

**Disclosures:** **Y. Horinaka:** None. **T. Urakawa:** A. Employment/Salary (full or part-time): Mazda Motor Corporation. **T. terunuma:** None. **K. Takahashi:** None. **S. Atarashi:** None. **T. kambara:** None. **O. Araki:** None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.11/MM1

**Topic:** I.04. Executive Functions

**Support:** NIH R37-NS128416

**Title:** Action restraint as a feedback-dependent control process in marmosets

**Authors:** \***E. A. TAECKENS**<sup>1</sup>, R. SHADMEHR<sup>2</sup>;

<sup>1</sup>Biomed. Engin., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; <sup>2</sup>Dept Biomed. Eng, Johns Hopkins Univ., Baltimore, MD

**Abstract:** Impulsivity, or the inability to withhold instinctive actions, is a symptom of many common psychiatric disorders, such as schizophrenia and ADHD. Numerous cortical and subcortical structures have been shown to be important for action restraint, but the specific computational functions implemented by these structures remain unclear. In this study, we aim to reveal the computational principles that enable action restraint in order to better characterize disorders of inhibitory control and to guide future research on the underlying neural mechanisms. We trained a marmoset (*Callithrix Jacchus*, male age 7 years) to perform a delayed saccade task that requires motor inhibition. The marmoset was prompted to fixate his eyes on a central target while a peripheral target appeared; he was trained not to look at the peripheral target until the central target disappeared. The fixation duration was varied (100-800 ms). Upon successful completion of fixation and the subsequent saccade, the marmoset received a food reward. We recorded 9,343 saccades across 4 sessions to quantify the distribution of saccade reaction times. Our results indicate that action restraint is an active, dynamic process that is regulated by internal feedback. We show that the marmoset's ability to restrain action is subject to rapid adjustments: saccades that followed premature attempts had higher average reaction time (Wilcoxon rank-sum test,  $p = 5e-9$ ) and probability of successfully holding (Two-proportion z-test,  $p = 1e-12$ ) compared to saccades that followed successful attempts. Additionally, the reaction time distribution was inconsistent with the interactive race model, a model that has frequently been used to explain the process of cancelling an impending action (Kolmogorov-Smirnoff test,  $p =$

2e-31). Instead, the distribution of reaction times was more accurately modeled by a noisy threshold crossing process with negative feedback. We tested the validity of this model with a second experiment in which the marmoset made saccades to two different targets, one of which was less visually salient than the other, resulting in increased reaction times. Despite only fitting the model to the high saliency trials, the feedback model generalized well to low saliency trials, with significantly higher log-likelihood than shuffled controls (permutation test,  $p < 1e-3$ ). These results suggest that impulsivity disorders may arise due to either mis-calibrated feedback gain or improper internal state estimation. Additionally, the results will inform future neurophysiological studies on action restraint in primates, which should search for neural mechanisms that can implement this feedback process.

**Disclosures:** E.A. Taeckens: None. R. Shadmehr: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.12/MM2

**Topic:** I.04. Executive Functions

**Support:** the Joint Usage/Research Program of the Center for the Evolutionary Origins of Human Behavior, Kyoto University 2025-031

**Title:** The mapping of response inhibition function in the prefrontal cortex using marmosets.

**Authors:** \*Y. KIM<sup>1</sup>, S. ISHIGAKI<sup>1</sup>, K. NAKAMURA<sup>2</sup>;

<sup>1</sup>Mol. Neurosci. Ctr., Shiga Univ. of Med. Sci., Otsu Shiga, Japan; <sup>2</sup>EHUB, Kyoto Univ., Inuyama, Japan

**Abstract:** Dementia, including Alzheimer's disease, and psychiatric disorders, such as depression and schizophrenia, are associated with a decline in various cognitive functions. A decline in response inhibition, the ability to inhibit inappropriate behavior, is a serious social problem because it significantly reduces patients' quality of life. Although marmosets have been utilized in medical and neuroscience research, the mapping of cognitive function in the marmoset prefrontal cortex is a relatively recent development. In this study, we conducted experiments to identify prefrontal regions involved in response inhibition. Three marmosets (*Callithrix jacchus*) performed a Go/No-Go task. This task required the marmosets to respond as quickly as possible to a Go stimulus and inhibit their response to a No-Go stimulus. This task has been used to examine response inhibition as it relates to prefrontal function. After learning the task, the marmosets received an injection of either a drug (muscimol; 0.1  $\mu$ g dissolved in 0.5  $\mu$ L) or saline (0.5  $\mu$ L) into the prefrontal cortex. This injection suppresses neural activity in specific regions in a reversible manner. After the injections, the marmosets were returned to their cages, and a short time later, they performed a Go/No-Go task. The muscimol and saline injection sites were in the dorsolateral area of the prefrontal cortex. Their performance on the cognitive task after

administration was then compared among the injection sites and between the muscimol and saline. Following the injection of muscimol, a change in the percentage of correct responses was observed.

**Disclosures:** Y. Kim: None. S. Ishigaki: None. K. Nakamura: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.13/MM3

**Topic:** I.04. Executive Functions

**Support:** RS-2022-NR070240  
RS-2023-00217361

**Title:** Phase preservation of EEG reflects distraction control of visual working memory

**Authors:** \*H. LEE<sup>1</sup>, M.-S. KANG<sup>1,2</sup>;

<sup>1</sup>Dept. of Psychology, Sungkyunkwan Univ., Seoul, Korea, Republic of; <sup>2</sup>Ctr. for Neurosci. Imaging Research, Inst. for Basic Sci. (IBS), Suwon, Korea, Republic of

**Abstract:** Distractor resistance is a hallmark of working memory. However, how working memory can tolerate distraction remains as an area to be explored. To examine the processes involved in distractor control, we designed two blocks of delayed color estimation task. In the first block and one-third trials of the second block, participants remembered the colors of two or four targets and reported one of them after a short period of retention interval. In the other two-third trials of the second block, distractors that have high- or low-impact were presented in the middle of retention interval. To manipulate their distraction magnitude, we assigned task-relevant features to high-impact distractors (colored digits), but not to low-impact distractors (black digits). Participants showed a better performance when two targets were present than four targets were present. Even though high-impact distractors damaged the performance under both set sizes, low-impact distractors disturbed performance only when set size was four. To examine cognitive processes of distractor control, we obtained phase coherence in theta-band oscillation; EEG phase preservation across trials. Distractors as well as targets evoked theta-band phase coherence at frontal and parietal electrodes which remained elevated after withdrawing distractors. Specifically, low-impact distractors elicited higher coherence than high-impact distractors when participants maintained two targets but comparable coherence when four targets were maintained. Additionally, phase coherence at the parietal electrode after distractor withdrawal was positively correlated with individual visual working memory capacity, measured independently; participants with higher capacity showed greater coherence after distractors were withdrawn. Taken together, phase coherence at the parietal electrode indicates distractor control process in visual working memory.

**Disclosures:** H. Lee: None. M. Kang: None.

**Poster**

**PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.14/MM4

**Topic:** I.04. Executive Functions

**Support:** The Fondation Bertarelli Graduate Fellowship  
T32MH020016  
Stanford Medicine Fellowship

**Title:** Exploring the effects of cognitive behavioral therapy on cognitive control circuit and behavioral task performance in hoarding disorder

**Authors:** \***P. A. MUNOZ RODRIGUEZ**<sup>1</sup>, **A. PINES**<sup>1</sup>, **X. ZHANG**<sup>2</sup>, **P. VAN ROESSEL**<sup>1</sup>, **P. MUKUNDA**<sup>1</sup>, **L. M. WILLIAMS**<sup>1</sup>, **C. I. RODRIGUEZ**<sup>3</sup>;  
<sup>2</sup>Dept. of Psychiatry and Behavioral Sci., <sup>1</sup>Stanford Univ., Stanford, CA; <sup>3</sup>Psychiatry and Behavioral Sci., Stanford Univ. Sch. of Med., Stanford, CA

**Abstract:** *Hoarding disorder (HD) is characterized by difficulty discarding or parting with possessions and clutter, which causes distress or impairment in important areas of functioning. Cognitivebehavioral therapy (CBT) for HD has shown promise; however, little is known about the brain mechanisms underlying symptom reduction. We previously reported the robust clinical effects of the Buried in Treasures workshop, a skills-based group, combined with using CBT principles augmented with uncluttering home visits (BIT+), in a waitlist-controlled trial involving adult with HD. This study examined neural activity in the cognitive control network in a subset of HD participants (n = 19) before and after 18 weeks of BIT+ sessions during a response inhibition task in an fMRI scanner. We used a comparison group of healthy controls (HC; n = 49). Participants in the HD group did not show more errors of commission than HC but made more errors of omission while performing the task. Neuroimaging findings indicated a correlation between improvements in hoarding symptoms and blood-oxygen-level-dependent (BOLD) signal during errors of commission in the right insula and anterior cingulate cortex of post-treatment HD participants, suggesting that changes in this region may be associated with the effectiveness of BIT+ treatment. This is the first study exploring neural activity changes associated with symptom-neutral inhibitory control before and after BIT+ treatment in a HD population.*

**Disclosures:** **P.A. Munoz Rodriguez:** None. **A. Pines:** None. **X. Zhang:** None. **P. van Roessel:** None. **P. Mukunda:** None. **L.M. Williams:** None. **C.I. Rodriguez:** None.

**Poster**

**PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H



**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.15/MM5

**Topic:** I.04. Executive Functions

**Support:** SECIHTI Mexico Scholarship 813946 to NLQ  
SECIHTI Mexico Posdoc 391161 to AGG

**Title:** Effect of passive musical stimulation on alpha power and executive function: evidence in neurotypical children

**Authors:** \*N. LAUREAN QUIROGA<sup>1</sup>, A. G. GUTIERREZ<sup>2</sup>, G. A. CORIA-AVILA<sup>3</sup>, D. HERRERA-COVARRUBIAS<sup>4</sup>, R. TOLEDO-CARDENAS<sup>4</sup>, G. E. ARANDA-ABREU<sup>7</sup>, M. HERNANDEZ<sup>5</sup>, J. MANZO<sup>6</sup>;

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**Abstract:** Passive musical stimulation has been proposed as a non-invasive intervention that modulates cortical dynamics and enhances attentional regulation. This study investigated the effect of repeated exposure to structured classical music on alpha-band cortical activity (8-12 Hz) and executive function performance in neurotypical children. Ten children aged 10 to 13 were randomly assigned to either an experimental (n=5) or control group (n=5). The experimental group received twelve weekly sessions of passive listening to Mozart's Sonata K.448, while the control group received no musical intervention. EEG recordings were obtained during eyes-closed rest in three conditions per session: baseline, music listening and post stimulation. The Stroop interference task was administered weekly in both groups; the experimental group completed it after music exposure, and the control group without prior stimulation. Alpha band power was quantified at bilateral electrode sites (AF3/AF4, F3/F4, F7/F8, FC5/FC6, P7/P8, T7/T8, O1/O2) using a 14 channel wireless EEG system (Emotiv Epoc X), and analyzed using repeated-measures ANOVA. Results showed a significant session-dependent decrease in alpha power ( $p < .05$ ) with a consistent pattern of right-hemisphere dominance. Additionally, the experimental group demonstrated selective improvements in inhibitory control as measured by the Stroop interference task. These findings suggest that passive musical stimulation may promote functional neuroplasticity associated with improved attention and executive regulation, with potential translational relevance to neurodevelopmental disorders such as autism spectrum disorder (ASD).

**Disclosures:** N. Laurean Quiroga: None. A.G. Gutierrez: None. G.A. Coria-Avila: None. D. Herrera-Covarrubias: None. R. Toledo-Cardenas: None. G.E. Aranda-Abreu: None. J. Manzo: None.

**Poster**

**PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.16/MM6

**Topic:** I.04. Executive Functions

**Support:** Ajman University-2023-IRG-MED-7

**Title:** Whole-body vibration therapy boosts cognitive speed while maintaining autonomic balance: A Stroop-ECG study

**Authors:** \*Z. HEIN<sup>1</sup>, N. SHANTAKUMARI<sup>2</sup>, C. CHE MOHD NASSIR<sup>3</sup>;

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**Abstract: Background:** Whole-Body Vibration Therapy (WBVT) is increasingly recognized as a promising alternative exercise modality with established benefits for musculoskeletal and cardiovascular health. However, its influence on cognitive function and autonomic nervous system activity in healthy individuals remains relatively unexplored. **Objective:** This study aimed to investigate the acute effects of WBVT on cognitive performance and autonomic responses in healthy young adults using a within-subjects experimental design. **Methods:** Thirty-six healthy volunteers (aged 18-25 years) completed two experimental sessions: a baseline (sedentary) session and an intervention session involving a 10-minute WBVT protocol. Cognitive performance was evaluated pre- and post-session using a Modified Stroop Test. Electrocardiographic recordings were used to assess heart rate variability (HRV) parameters, including mean heart rate and stress index, at baseline, during the Stroop task, and post-intervention. Data were analyzed using paired-sample t-tests and repeated measures ANOVA. **Results:** WBVT significantly improved reaction times across total, congruent, and incongruent Stroop conditions ( $p < 0.001$ ), without compromising response accuracy. The Stroop interference score remained unchanged. A marginal increase in the stress index was observed during the Stroop task ( $p = 0.052$ ), which normalized post-WBVT. No significant changes were observed in HRV parameters, including low frequency (LF), High frequency (HF), and LF/HF ratio. **Conclusion:** WBVT may enhance cognitive processing speed without inducing autonomic imbalance, supporting its potential as a non-pharmacological strategy to improve cognitive performance in healthy individuals. **Keywords:** Whole-Body Vibration Therapy, Cognitive Function, Heart Rate Variability, Stroop Test, Executive Function

**Disclosures:** Z. Hein: None. N. Shantakumari: None. C. Che Mohd Nassir: None.

**Poster**

**PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.17/MM7

**Topic:** I.04. Executive Functions

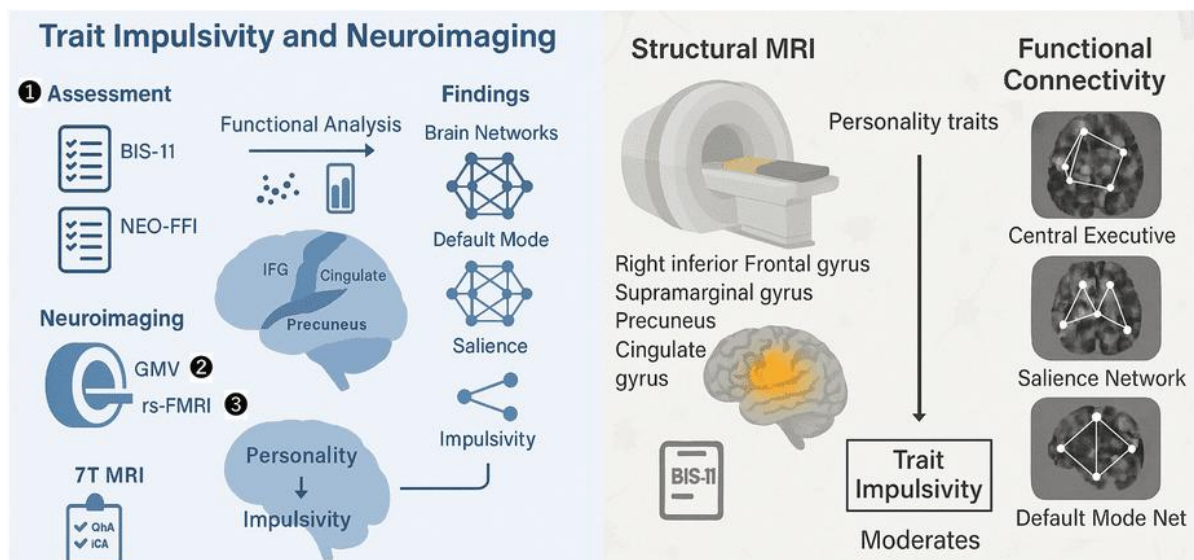
**Support:** JST

**Title:** Ultra-high-field 7T MRI reveals structural and functional correlates of trait impulsivity

**Authors:** \*Y. JIANG<sup>1</sup>, H. FUJIWARA<sup>2</sup>, T. MURAI<sup>2</sup>, A. SAWA<sup>3</sup>;

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**Abstract:** Impulsivity is a transdiagnostic trait implicated in various psychiatric disorders, including ADHD, depression, PTSD, and personality disorders. However, the neural substrates of trait impulsivity and their interaction with personality traits remain incompletely understood. Using ultra-high-field 7T MRI, we investigated gray matter volume (GMV) and resting-state functional connectivity (rsFC) correlates of trait impulsivity in 104 healthy adults (mean age = 35.3 years; 56 males). Trait impulsivity was assessed via the Barratt Impulsiveness Scale-11 (BIS-11), which captures both classical (motor, attentional, non-planning) and alternative (reward delay intolerance, rapid response) dimensions. Partial correlations controlling for age and sex revealed positive associations between impulsivity and GMV in the right inferior frontal gyrus, right supramarginal gyrus, left precuneus, and right cingulate gyrus. Functional connectivity analyses implicated the central executive, salience, and default mode networks, highlighting disrupted cognitive control and salience processing in impulsive individuals. Personality traits also showed significant associations: neuroticism positively correlated with impulsivity, while conscientiousness, agreeableness, and extraversion showed negative associations, suggesting a moderating role. Findings were consistent across two brain atlases (Ipba40, Schaefer2018-100Parcels-17Networks). These results support a neurobiological model in which structural and functional brain alterations underpin trait impulsivity, moderated by personality, with implications for dimensional models of psychiatric disorders. Ongoing work integrates voxel-based morphometry with independent component analysis to elucidate transdiagnostic mechanisms of impulsivity.



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**Poster**

**PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.18/MM8

**Topic:** I.04. Executive Functions

**Support:** U19AG078109

**Title:** Cross-sectional model and predictors of cognitive resilience in an ethnoracially diverse cohort

**Authors:** \*M. W. HAND<sup>1</sup>, Z. TSOKOLAS<sup>1</sup>, K. V. WHEELER<sup>1</sup>, V. TENNANT<sup>1</sup>, N. LEE<sup>1</sup>, A. CLARK<sup>2</sup>, S. O'BRYANT<sup>3</sup>, A. W. TOGA<sup>4</sup>, K. YAFFE<sup>5</sup>, M. BRASKIE<sup>1</sup>;

<sup>1</sup>Keck Sch. of Medicine, Univ. of Southern California, Marina del Rey, CA; <sup>2</sup>Univ. of Texas, Austin, TX; <sup>3</sup>Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX; <sup>4</sup>USC Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA; <sup>5</sup>Univ. of California San Francisco, San Francisco, CA

**Abstract:** Cognitive resilience is the potential to resist cognitive decline in the presence of Alzheimer's Disease (AD) pathology. We investigated which features in cognitively unimpaired older adults best explain cognitive performance given brain amyloid, tau, and neurodegeneration after controlling for age and years of education.

We included 775 cognitively unimpaired (127 Hispanic, 303 non-Hispanic Black; NHB, and 345 non-Hispanic White; NHW) adults from the Health and Aging Brain Study-Health Disparities (HABS-HD) cohort (65% female, aged 50 - 90; mean 65). Cognitive Composite Scores (CCS) were calculated using a mean of z-scored values from: MMSE, Logical Memory Delayed Recall, Trail Making Test Part B Total Time, Spanish-English Verbal Learning Delayed Recall, and Category Fluency (Boyle et al, 2024). In 70% of our sample, we trained a linear regression model to predict CCS using global amyloid (Florbetaben PET), medial temporal lobe tau (PI-2620 PET), cortical thickness in an Alzheimer's disease sensitive meta-ROI (entorhinal cortex, fusiform gyrus, and inferior and middle temporal cortex), years of education, and age. The resulting model was applied to the test set (30% of our sample) to estimate predicted CCS and cross-validated across ten randomized seeds. A multiple linear regression was used to investigate whether self-reported ethnoracial identity, sex, diabetes diagnosis, hypertension, dyslipidemia, education quality (American Version of National Adult Reading Test; AMNART), bilingualism, or annual household income related to actual minus predicted cognitive performance (cognitive residuals).

NHW (median  $\beta = 0.22$ ,  $p < 0.05$  10/10 times) participants showed higher cognitive residuals compared to NHB participants, while cognitive residuals in Hispanic participants did not differ from either group. Of the remaining variables, only higher AMNART (median  $\beta = 0.13$ ,  $p < 0.05$  10/10 times) and female sex (median  $\beta = 0.17$ ,  $p < 0.05$  8/10 times) were associated with higher

cognitive residuals in  $\geq 7/10$  iterations. Calculated CCS and trained CCS models showed mean RMSE = 0.48 and  $R^2 = 0.18$ . We found higher cognitive residual values (better-than-expected cognitive performance) in NHW participants, with education quality associated with higher scores in all groups. Higher cognitive resilience in women was consistent with previous literature. Possibly, differences between ethnoracial identities result from neurodegeneration or tau in NHB participants across brain regions not measured, a target of future investigation. Cognitive resilience, as a construct, should be further examined among diverse communities.

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## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.19/MM9

**Topic:** I.04. Executive Functions

**Support:** Azrieli Foundation

**Title:** The role of executive functions in coping with endometriosis and improving quality of life: a pilot study

**Authors:** \*S. KHATIB<sup>1</sup>, H. HASSAN<sup>2</sup>, A. REISS<sup>2</sup>, B. ENGEL YEGER<sup>1</sup>;

<sup>1</sup>Dept. of Occup. Therapy, Fac. of Social Welfare and Hlth. Sci., Univ. of Haifa, Haifa, Israel;

<sup>2</sup>Dept. of Obstetrics and Gynecology, Emek Med. Ctr., Afula, Israel

**Abstract:** Endometriosis is a chronic gynecological condition associated with physical and emotional burden, which reduce quality of life (QOL). Therefore, efficient strategies are critical for coping with endometriosis impacts. Coping strategies are related to the high cognitive abilities named "Executive functions" (EF). EF encompasses the capacity to plan, regulate, and adapt behavior. Yet, the relations between EF, coping, and QOL in women with endometriosis remain understudied. We aimed to: (1) compare EF, coping strategies and QOL between women with endometriosis and healthy controls. (2) examine the relationships between EF, coping strategies and QOL among women with endometriosis. This pilot study included 67 women (16 with clinically confirmed endometriosis, 60 age-matched healthy controls) completed the Barkley Deficits in Executive Functioning Scale-Short Form (BDEFS-SF), the COPE inventory and the WHOQOL-BREF. Group comparisons were assessed using the Mann-Whitney U test; associations between EF, coping, and QOL were analyzed with Spearman's correlations. Women with endometriosis demonstrated significantly greater EF deficits ( $p < .001$ ), greater reliance on coping strategies, those involving avoidance and denial ( $p = .034$ ) and lower QOL ( $p < .001$ ). Among women with endometriosis greater EF deficits strongly correlated with lower QOL women with ( $\rho = -.773$ ,  $p < .001$ ). Denial/avoidance coping significantly correlated with

reduced QOL ( $\rho = -.718$ ,  $p = .004$ ). Further studies should examine the role of EF and coping in improving QOL of women with endometriosis. Support of the present study results will emphasize that intervention should address EF and coping to improve patients' QOL. Intervention should incorporate a vast perspective and refer to the interactions between the disease and factors that may improve daily functioning and QOL.

**Disclosures:** S. Khatib: None. H. Hassan: None. A. Reiss: None. B. Engel Yeger: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.20/MM10

**Topic:** I.04. Executive Functions

**Support:** San Diego State University

**Title:** Neural and behavioral indices of decision-making in people with fibromyalgia are age-dependent

**Authors:** \*Y. EPIR<sup>1</sup>, M. MARVIN<sup>2</sup>, D. WHITE<sup>1</sup>, T. A. CRONAN<sup>1</sup>, K. MARINKOVIC<sup>1,2</sup>;  
<sup>1</sup>Psychology, San Diego State Univ., San Diego, CA; <sup>2</sup>SDSU / UCSD Joint Doctoral Program, San Diego, CA

**Abstract:** Fibromyalgia (FM) is a chronic pain condition characterized by widespread musculoskeletal pain, which is frequently accompanied by fatigue, cognitive impairments, insomnia, and other symptoms. With no clear causative peripheral pathology, FM is considered a centralized pain disorder, presenting a challenge for diagnostic and treatment strategies. Impaired cognitive control is common in individuals with chronic pain, implicating difficulties with executive functions more broadly. Cognitive control refers to the capacity to suppress automatic responses in favor of prioritizing goal-directed, non-habitual behaviors to enhance adaptive decision-making. This study examined the neurobehavioral characteristics of cognitive control in 38 people diagnosed with FM and 29 control (CONT) participants who were matched on demographic variables and cognitive capacity. Participants were additionally subdivided into groups of young (YA,  $24.3 \pm 4$ ) and older adults (OA  $53.1 \pm 8$ ). After a neuropsychological evaluation, participants engaged in a modified Stroop color-word interference task that elicited a low or high level of cognitive conflict by presenting words in fonts that were congruent or incongruent with their meaning (e.g., "RED" written in red or blue, respectively). Electroencephalography (EEG) signals were analyzed in the time-frequency domain in theta band (4-7 Hz), which is highly sensitive to cognitive control engagement. The EEG data were also analyzed in the time domain as event-related potentials (ERPs). The people with FM maintained equivalent performance accuracy as the CONT group but at the cost of longer reaction times (RT), especially on high-conflict trials. Similarly, OA participants exhibited a general RT slowing. Event-related theta power (ERTP) was lower as a function of group (FM

lower than CONT) and age (OA lower than YA), which was particularly notable during high cognitive conflict. In the FM group, lower ERTP was associated with longer RTs, more severe pain-related dysfunction, and higher depression scores. ERP analysis was broadly consistent with ERTP findings, but it revealed a delayed engagement of cognitive control in people with FM and in OA with greater temporal precision. Taken together, these results suggest dysregulated neural mechanisms underlying cognitive control in people with FM and in OA. They align with neuroimaging evidence suggesting dysfunctional top-down neuromodulation relevant to chronic pain and age. The study provides insight into the neural indices that may aid in diagnostic, prognostic, and treatment-monitoring purposes, ultimately helping to develop targeted therapies.

**Disclosures:** Y. Epir: None. M. Marvin: None. D. White: None. T.A. Cronan: None. K. Marinkovic: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.21/MM11

**Topic:** I.04. Executive Functions

**Title:** Delirium Rates in Medically Underserved Versus Medically Well-Served Populations in Central Missouri

**Authors:** \*A. I. KHREIS<sup>1</sup>, D. S. BHANDAL<sup>1</sup>, K. SINGH<sup>3</sup>, M. SANDHU<sup>3</sup>, J. A. VALLEJO<sup>2</sup>, M. A. RODRIQUEZ<sup>1</sup>;

<sup>2</sup>Biomed. Sci., <sup>1</sup>UMKC Sch. of Med., Kansas City, MO; <sup>3</sup>Alabama Col. of Osteo. Med., Dothan, AL

**Abstract:** Delirium is an abrupt onset of cognitive dysfunction (1) and is frequently associated with poor short- and long-term health outcomes. Previous investigations into associations between medically underserved populations and delirium rates are scarce; however, they indicate that socioeconomic status may play a role (1). Income is a major social determinant of health and influences whether patients can afford private insurance or qualify for public insurance. Previous studies have demonstrated aspects of diminished access to healthcare for patients on public insurance when compared to privatized insurance (2). This exploratory study aims to identify disparities in rates of delirium between medically underserved populations with either public insurance or self-pay status and medically well-served populations with private insurance. We predicted rates of delirium would vary over time across the general population in patients under the age of 65, stratified by patient payment type (private insurance, public insurance, or private funds). Using the University of Missouri Informatics for Integrating Biology and the Bedside (i2b2) records, we evaluated the rates of delirium with respect to patient insurance and age group from 2015-2025. Most patients were treated in Central Missouri. The patients were classified as having private insurance, public insurance such as Medicaid and Medicare, as well as those who used private funds to pay for healthcare. The data showed that rates of delirium varied by

insurance payment type, with the highest rates observed in patients with public insurance, followed by those who used private funds, and the lowest rates among patients with private insurance. Regarding time, there was a slight decrease in delirium rates in patients under 65. Overall, our study finds that delirium rates vary by type of insurance. Furthermore, patients who are medically underserved appear to experience higher rates of delirium, while those who are medically well-served tend to have lower rates.

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1. Khanna, A., Govil, M., Ayele, N., & Saadi, A. (2024, August). Disparities in Delirium across the Continuum of Care and Associations with Social Determinants of Health. In *Seminars in Neurology*. Thieme Medical Publishers, Inc..
2. Hsiang, W. R., Lukasiewicz, A., Gentry, M., Kim, C. Y., Leslie, M. P., Pelker, R., ... & Wiznia, D. H. (2019). Medicaid patients have greater difficulty scheduling health care appointments compared with private insurance patients: a meta-analysis. *INQUIRY: The Journal of Health Care Organization, Provision, and Financing*, 56, 0046958019838118.

**Disclosures:** A.I. Khreis: None. D.S. Bhandal: None. K. Singh: None. M. Sandhu: None. J.A. Vallejo: None. M.A. Rodriquez: None.

#### Poster

##### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.22/MM12

**Topic:** I.04. Executive Functions

**Title:** Cognitive impairment in individuals with chronic spinal cord injury: a verbal fluency task-based functional magnetic resonance imaging study

**Authors:** \*J. SRITHARAN<sup>1</sup>, V. VALLESI<sup>1</sup>, L. DIANA<sup>1</sup>, V. MORO<sup>2</sup>, G. A. ZITO<sup>1</sup>;

<sup>1</sup>Swiss Paraplegic Res., Nottwil, Switzerland; <sup>2</sup>Dept. of Human Sci., Univ. of Verona, Verona, Italy

**Abstract: Introduction:** Individuals with spinal cord injury (SCI) are subject to a substantially high risk of cognitive impairment, with executive functions being among the most affected ones. Even though the occurrence of cognitive impairment following SCI has been confirmed in several studies, the underlying mechanisms in the brain are not known yet. This study aims to tackle this issue, by investigating the neural correlates of executive functions in SCI. **Methods:** 26 individuals with chronic SCI (mean age=45.8± 11.0, mean time since injury=13.3± 11.1 years) and 26 non-injured controls (mean age=43.1± 11.5 years) were recruited. During the functional magnetic resonance imaging (fMRI) measurement, participants performed a phonemic verbal fluency task. The sum of correct words across all letters was considered as indicator of phonemic verbal fluency. Group differences in brain activity and seed-based functional connectivity (FC) were tested with a general linear model. Seeds included regions typically



associated with phonemic verbal fluency. Moreover, FC was correlated with verbal fluency performance using Pearson's correlation. **Results:** Performance in the verbal fluency task was significantly lower (15% less correct words) in SCI compared to non-SCI individuals ( $p=0.02$ ). Brain activity was significantly lower in the basal ganglia in individuals with SCI ( $p=0.015$ , corrected with family-wise error - FWE). There was lower FC between the left insula and left superior frontal gyrus in SCI compared to non-injured controls ( $p<0.001$ , FWE). In SCI only, verbal fluency performance negatively correlated with FC between right insula and postcentral gyrus ( $r=-0.82$ ,  $p=0.001$ , FWE), and between left putamen and bilateral precentral gyrus ( $r=-0.74$ ,  $p=0.002$ , FWE). **Conclusions:** Altered brain activity in the basal ganglia may imply that the inhibition of irrelevant words is affected in individuals with SCI. Moreover, FC was altered in regions typically involved in executive functions. As the insula is switching between brain networks, including the central executive network, to allocate cognitive resources, its altered FC with prefrontal areas may be linked to deficits in executive functions in SCI. Moreover, the FC of sensorimotor regions negatively correlated with verbal fluency performance, suggesting that the disrupted sensorimotor network in SCI may interfere with cognitive functions.

**Disclosures:** J. Sritharan: None. V. Vallesi: None. L. Diana: None. V. Moro: None. G.A. Zito: None.

## **Poster**

### **PSTR242: Inhibitory Control and Disorders of Executive Functions**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR242.23/MM13

**Topic:** I.04. Executive Functions

**Support:** NIH 1R01NS094444  
UB SPARC Award

**Title:** Including the brainstem in a neuroimaging investigation of sports-related concussion

**Authors:** \*E. CASTRO<sup>1</sup>, F. SCHWESER<sup>2</sup>, S. E. MULDOON<sup>3</sup>, J. LEDDY<sup>1</sup>, M. N. HAIDER<sup>4</sup>;  
<sup>1</sup>SUNY Buffalo, Buffalo, NY; <sup>2</sup>Neurol., Univ. at Buffalo, The State Univ. of New York, Buffalo, NY; <sup>3</sup>Dept. of Mathematics, State Univ. of New York, Univ. at Buffalo, Buffalo, NY;  
<sup>4</sup>Orthopedics, Univ. at Buffalo, Buffalo, NY

**Abstract:** Sports-related concussions (SRC) are a public health concern. Although SRC typically shows no abnormalities on standard neuroimaging, advanced methods such as diffusion magnetic resonance imaging (dMRI) can examine microstructural changes post SRC. While some studies have assessed SRC-associated microstructural changes, the brainstem is often excluded in these investigations. However, the brainstem is known to be particularly vulnerable to SRC damage due to its location in the brain, and by excluding it from analyses, we may not get a full understanding of SRC brain changes. Here we specifically include the brainstem to characterize whole brain microstructural and network changes in adolescent athletes with SRC. We assess

individual variability in 35 adolescent athletes with SRC and 34 control athletes, using multishell dMRI data collected within 10 days of injury (recruitment for controls) and after clinical recovery (4 to 6 weeks after recruitment for controls). Data was pre-processed, registered to a population-specific atlas, and tractography was performed. Diffusion and network measures were calculated to assess microstructural and network changes, respectively. Further, differential tractography was performed to assess individual differences in brain structure resulting from SRC. When examining microstructural changes, we found that females had significantly higher mean and radial diffusivity, indicative of increased water diffusion and demyelination. At the network level, females had significantly higher clustering coefficient and global dissimilarity, which measure local interconnections and network similarity, respectively. When using differential tractography to detect changes in tract integrity over time, male concussed athletes exhibited a higher number of injured tracts, while female concussed athletes showed minimal differences from controls. We also found that brainstem tracts such as the corticospinal and corticobulbar tracts were consistently detected as being injured post SRC. These results corroborate sex differences found in prior neuroimaging studies of SRC and agree with biomechanical studies that have determined the brainstem to be vulnerable to the effects of a concussion. It is therefore important that future neuroimaging studies include the brainstem in their analyses to gain a comprehensive understanding of SRC damage.

**Disclosures:** E. Castro: None. F. Schweser: None. S.E. Muldoon: None. J. Leddy: None. M.N. Haider: None.

## **Poster**

### **PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.01/MM14

**Topic:** I.06. Social Cognition

**Support:** Yale Department of Psychiatry

**Title:** Communal drumming decreases autonomic response, stress, and anxiety

**Authors:** \*D. A. WATTS<sup>1</sup>, K. ADICHIE<sup>1,2</sup>, C. S. AKAFIA<sup>1</sup>, S. DAYAL<sup>1</sup>, G. A. ALAYINE<sup>1</sup>, A. ALLSOP<sup>1,2</sup>;

<sup>1</sup>Dept. of Psychiatry, Yale Univ., New Haven, CT; <sup>2</sup>Dept. of Psychiatry and Behavioral Sci., Howard University, Ctr. for Collective Healing, Washington, DC

**Abstract:** Introduction: Social connection is imperative to human health and wellbeing.<sup>1</sup> Music, particularly practiced in communal forms, has been shown to increase pro-social behavior and overall quality of life.<sup>2</sup> However, further research is necessary to explore the mechanisms behind this relationship. This study investigates the impact of communal drumming on autonomic physiology and quality-of-life measures such as anxiety and perceived stress. We hypothesize that communal drumming will decrease anxiety and perceived stress and increase feelings of

connectedness and altered states of consciousness. Methods: Participants took part in either (a) a single communal drum circle (n=19) or (b) a weekly communal drum circle for eight weeks (n=47). There were two instances of experiment (a) between which the structure differed slightly at the facilitator's discretion. The structure of experiment (b) was constant between sessions, spanning 40 minutes. While the facilitators differed between the two experiments, they remained consistent throughout the experiment. In experiment (a), heart rate data were collected and segmented according to periods of distinct activity. These data were averaged and compared via an ANOVA and correlated with psychometric data. Psychometric survey data were gathered in both experiments. Results: Compared to control conditions, participants (n = 15) in experiment (a) during rhythmic variation conditions showed decreased standard deviation of normal-to-normal (SDNN) intervals, which was significantly correlated with decreased self-reported anxiety levels ( $p < .05$ ). In one drum circle session (n = 9), we found decreased SDNN intervals during communal drumming session ( $p < .05$ ). Psychometric data from experiment (b) further revealed a decrease in participants' (n = 43) self-reported acute distress across the 8 -week intervention ( $p < .05$ ). Conclusion: These results indicate that distinct musical conditions: synchronous drumming, rhythmic variations, and collective layering of distinct rhythmic patterns, elicit differential autonomic responses reflecting condition specific physiological changes. These findings suggest that participating in communal drumming decreases autonomic stress responses, anxiety, and perceived stress and increases altered states of consciousness. This work contributes to limited literature proposing a physiological and neurological mechanism for healing through communal rhythmic practices.<sup>3</sup> 1 Proctor, A.S. et al. (2023) Lifestyle Medicine, 4(4): p. e91 2 Wu, H., et al. (2025) Frontiers in Psychology, 15: p. 1453808. 3 Aaron, M. L. et al. (2012). 10.13140/RG.2.1.3956.4884

**Disclosures:** D.A. Watts: None. K. Adichie: None. C.S. Akafia: None. S. Dayal: None. G.A. Alayine: None. A. Allsop: A. Employment/Salary (full or part-time): Mefreely, LLC-cofounder.

## **Poster**

### **PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.02/MM15

**Topic:** I.06. Social Cognition

**Support:** Yale Department of Psychiatry

**Title:** Music therapy in high-stress and high-trauma populations reduces anxiety, increases social connectedness, and acutely alters autonomic and central nervous system activity

**Authors:** S. DAYAL<sup>1</sup>, \*D. RAYFORD<sup>2,1</sup>, D. A. WATTS<sup>1</sup>, C. S. AKAFIA<sup>1</sup>, G. A. ALAYINE<sup>1</sup>, P. TOOTLE<sup>1</sup>, J. DELINOIS<sup>1</sup>, C. RAMIREZ<sup>1</sup>, A. TURK<sup>1</sup>, A. ALLSOP<sup>1</sup>;

<sup>1</sup>Dept. of Psychiatry, Yale Univ., New Haven, CT; <sup>2</sup>Dept. of Psychiatry, Yale Sch. of Med., New Haven, CT

**Abstract:** *Introduction:* Individuals within the criminal justice system and recovery facilities face a higher burden of trauma<sup>1,2,3</sup> and stress<sup>4</sup> than the average population, but remain neglected in our approach to therapeutics<sup>5</sup>. Music-based activities (MBAs) have been linked to well-being and recovery by influencing physiological and neurological activity, emotional state, and social connection<sup>6</sup>. Despite evidence that group MBAs are effective in high-stress and high-trauma environments due to their accessible and connection-building nature<sup>7</sup>, their potential to address trauma and stress in a biologically-informed manner remains understudied. We worked with participants residing in 3 different carceral centres, a rehabilitation centre, and a residential treatment centre [N[s1] =66] to investigate the efficacy of MBAs in improving biological markers of connectedness, psychometric measures such as anxiety and stress, and perceived social connectedness in individuals with high trauma and stress levels. *Methods:* We used wearable technology to record electroencephalography (EEG) signals and heart rate variability data (HRV) from participants during an MBA. We also assessed the impact of the MBA on participants' perceptions of social connectedness based on surveys measuring their perceived familiarity, connection, approachability, socioeconomic similarity, shared political views, and willingness to compromise to solve a complex problem; which were assessed using a self-reported questionnaire completed once before and after the MBA. Lastly, we collected participants' self-reported scores on 5 difference psychometric scales such as the State Motivation to Foster Social Connectedness scale (SMFSC), Watts Connectedness Scale (WCS), Perceived Stress Scale (PSS), Absorption in Music Scale (AIMS), and Beck Anxiety Inventory (BAI). *Results and discussion:* Physiologically, we found significant differences between baseline and music from the MBA across two facilities at the Pz electrode for Delta, Theta and Alpha frequency bands. HRV analysis indicated decreases in SDNN during music therapy participation as well decreases in RMSSD. Psychometric and self-reported data indicated significant differences between pre- and post-MBA scores for questions about familiarity, connectedness, approachability, politics, controversial topics, and problem-solving. Participants' overall self-reported post-MBA connectedness scores (across the 7 questions) significantly increased when compared to pre-MBA scores. Importantly, we observed a significant decrease in Beck Anxiety Inventory (BAI) scores across all groups in the post-MBA condition.

**Disclosures:** S. Dayal: None. D. Rayford: None. D.A. Watts: None. C.S. Akafia: None. G.A. Alayine: None. P. Tootle: None. J. Delinois: None. C. Ramirez: None. A. Turk: None. A. Allsop: Other; Mefreely, LLC-cofounder..

## **Poster**

### **PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.03/MM16

**Topic:** I.06. Social Cognition

**Title:** Distinct Neural And Autonomic Pathways Underlie The Cognitive And Emotional Effects Of Indian Classical Music Scales

**Authors:** \*M. NANDIGAM<sup>1</sup>, C. S. K. AKAFIA<sup>2</sup>, G. A. ALAYINE<sup>3</sup>, C. RAMIREZ<sup>4</sup>, S. DAYAL<sup>4</sup>, F. HUSEYNOV<sup>4</sup>, S. A. ALLSOP<sup>1</sup>;

<sup>1</sup>Dept. of Psychiatry, <sup>2</sup>Psychiatry, <sup>3</sup>Yale Dept. of Psychiatry, <sup>4</sup>Yale Univ., New Haven, CT

**Abstract:** Indian classical music (ICM) is built on melodic scales, or ragas, traditionally attributed to distinct emotional and bodily states<sup>1</sup>. While ICM has shown physiological and cognitive benefits, the underlying mechanisms remain largely uncharacterized<sup>2,3</sup>. We examined the effects of three ragas—Darbari Kanada, Hamsadhvani, and Thodi—on brain activity, autonomic function, working memory, and emotion. We hypothesized that each raga produces a unique neurophysiological signature driving distinct cognitive and emotional outcomes. In a within-subjects design, 55 participants (Indian musicians = 11, Western musicians = 16, Indian non-musicians = 14, Western non-musicians = 14) listened to 7-min raga clips and a non-music control condition in randomized order. EEG and ECG were recorded via wearable sensors. Emotional responses and working memory performance was assessed before and after each condition via the digit span task. Each raga produced distinct multimodal effects (Figure 1). Darbari Kanada significantly enhanced working memory ( $q = 10.29$ ,  $p < 0.0001$ ), frontal theta power at AF3 ( $p < 0.0295$ ), and parasympathetic activity ( $q = 6.880$ ,  $p < 0.0001$ ), compared to all other ragas. Memory improvements correlated with RMSSD changes ( $p < 0.0001$ ), suggesting a shared autonomic-neural pathway. Hamsadhvani evoked the highest happiness ratings ( $p < 0.0001$ ) and increased alpha/theta power ( $p < 0.0001$ ). Thodi evoked negative affect but minimal cognitive or physiological change. No significant differences were observed based on musical training or cultural familiarity. Our findings support a sequence model in which ordered frequencies drive specific physiological and cognitive effects. The absence of familiarity-based differences suggests raga-based interventions may have broad applicability as a culturally informed, targeted therapy in treating cognitive decline and anxiety. <sup>1</sup>Sanivarapu, Sravanti L. (2015). *Indian Journal of Psychiatry* 57(2):p 210-213 <sup>2</sup>Balasubramanian G. et al (2024) *Cogn Neurodyn*. 18(3):829-845 <sup>3</sup>Babel, S. et al (2023). *Cureus*, 15(11), e49592

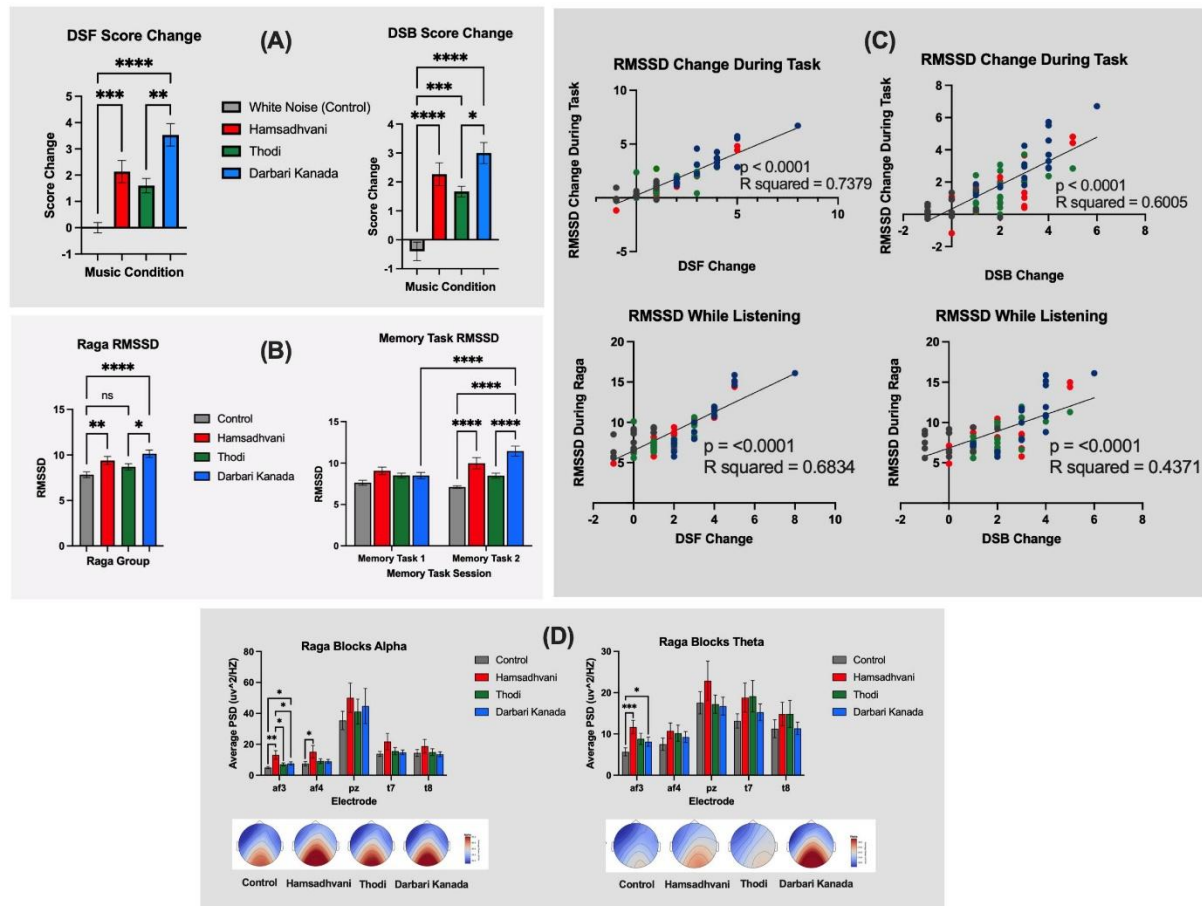


**Figure 1.** (A) Score changes on digit span forward (DSF) and digit span backward (DSB) tasks, separated by raga condition; (B) Parasympathetic activity (RMSSD) during each raga and during digit span tasks, separated by raga condition; (C) Linear correlations between RMSSD changes during memory task/during raga listening and digit span improvements, color-coded by raga condition; and (D) Average spectral density values at alpha and theta bands at all 5 electrodes during each raga condition.

**Disclosures:** M. Nandigam: None. C.S.K. Akafia: None. G.A. Alayine: None. C. Ramirez: None. S. Dayal: None. F. Huseynov: None. S.A. Allsop: None.

## Poster

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.04/MM17

**Topic:** I.06. Social Cognition

**Support:** Yale Department of Psychiatry  
Yale School of Medicine  
Howard University Department of Psychiatry and Behavioral Science  
New Haven Symphony Orchestra  
BLOOM in New Haven, CT  
Streaming CT Services

**Title:** Music Mindfulness Modulates Heart Rate and EEG Synchrony in Dyads

**Authors:** \*G. A. ALAYINE<sup>1</sup>, C. S. AKAFIA<sup>1</sup>, C. RAMIREZ<sup>1</sup>, K. ADICHIE<sup>1,2</sup>, D. A. WATTS<sup>1</sup>, S. SAEDI<sup>1</sup>, A. ALLSOP<sup>1,2</sup>;

<sup>1</sup>Dept. of Psychiatry, Yale Univ., New Haven, CT; <sup>2</sup>Dept. of Psychiatry and Behavioral Sciences, Ctr. for Collective Healing, Howard Univ., Washington, DC

**Abstract:** Synchrony is the reciprocal and adaptive behavior in dyadic interactions, manifesting across emotional, cognitive, motor, and physiological domains. Heart rate (HR) and neural data are physiological markers of synchrony that provide insight into temporal dynamics and structure of synchronization, elucidating its mechanistic underpinnings. In therapeutic contexts, synchrony gauges the strength of interpersonal connectedness and treatment effectiveness. Though examined in clinical settings such as in counselor-patient interactions, synchrony remains under-explored in community contexts. Community based music mindfulness intervention has demonstrated both psychological and physiological benefits. We hypothesize that a community based intervention such as music mindfulness, enhances synchrony and can be demonstrated physiologically through HR and neural synchrony. HR and EEG data from a total of 14 dyads, with varying degrees of familiarity, engaged in music mindfulness sessions for focus and motivation, were assessed for synchrony. We considered dyads who participated in the same sessions for a pairwise synchrony analysis. For HR, we used cross-recurrence plots (CRP) and cross-recurrence quantification analysis (CRQA) to generate patterns and quantify the interrelationships between each pair of R-R intervals derived from the HR data. The CRQA synchrony metrics that were computed include Recurrence Rate, Determinism, Laminarity, Entropy and Maximum Line. We evaluated neural synchrony (EEG) in focus sessions for 5 dyads by computing Phase Locking Value (PLV) introduced by Lachaux et. al 1999 for each frequency band in all dyads.

Preliminary results showed an increase in HR synchrony across focus sessions with music for 2 dyads and a decrease for 4 dyads. This also increased and decreased for 3 dyads each towards the end of no music sessions. During music for motivation sessions, we observed a consistent increase in HR synchrony for 4 dyads and a decrease in synchrony in 4 dyads at the end compared to the beginning of the sessions. Synchrony increased in 3 dyads and decreased in 5 dyads at the end as compared to the beginning during no music. PLV analysis showed no significant difference in PLV between focus based music and no music sessions. The mean PLV for each frequency band and channel ranged from 0.2 to 0.25, signaling no significant neural synchrony between dyads. While different patterns of synchrony were observed in both HR and EEG data, higher synchrony emerged towards the end of sessions in HR implying that music mindfulness may drive convergent physiology in dyads across sessions.

**Disclosures:** G.A. Alayine: None. C.S. Akafia: None. C. Ramirez: None. K. Adichie: None. D.A. Watts: None. S. Saedi: None. A. Allsop: Other; Mefreely, LLC-cofounder.

**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.05/MM18

**Topic:** I.06. Social Cognition

**Title:** Jamming as Meditation: Unpacking the neurophysiological relationship between improvisational music performance and mindfulness meditation flow states

**Authors:** \*C. JEWELL, E. L. STEGEMOLLER;  
Iowa State Univ., Ames, IA

**Abstract:** Qualitative interviews with professional improvising musicians inform us that when improvisation is going well, a state of flow is commonly identified by musicians as a key contributing factor. While many professional improvising musicians explicitly use the word “flow”, others will convey the experience by describing the state as “meditative” or “mindful” in conjunction with “flow”. Despite the conflation of flow states with mindfulness meditation during improvisational music performance, the scientific rationale and physiological basis for this conflation are limited. We examined electroencephalography (EEG) power spectra and heart rate variability (HRV) high and low frequencies associated with subjective flow states in experienced improvising musicians during group music improvisation and mindfulness meditation in a naturalistic setting using portable physiology devices. EEG power spectra were normalized to 1 for each electrode. Power spectra ratios will be obtained by dividing one spectrum by another, resulting in an F distribution. From the F table, critical values were obtained using the total number of epochs in each group as the degrees of freedom. Values falling outside of the critical values are considered a significant difference ( $\alpha = 0.05$ ) between power spectra. Preliminary results suggest that HRV is higher and that EEG power spectra differ during mindfulness meditation relative to music improvisation flow states. Taken together, this may suggest that the flow states during mindfulness meditation and improvisational music performance are different physiologically. Data collection is ongoing to confirm these preliminary results. Nonetheless, these results support as well as challenge the position that improvisational music performance and mindfulness meditation share neurophysiological similarities during a flow state experience.

**Disclosures:** C. Jewell: None. E.L. Stegemoller: None.

**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM



**Program #/Poster #: PSTR243.06/OO1**

**Topic:** I.06. Social Cognition

**Support:** FONDECYT 1170145  
FONDEQUIP Project EQM 150003  
PIA-CONICYT Basal Funds for Centers of Excellence Project FB0003  
ANID Support 2024 AFB240004

**Title:** Mutual Trust Drives Interbrain Coupling During Cooperative Interactions

**Authors:** \*P. BARRAZA<sup>1</sup>, E. RODRIGUEZ<sup>2</sup>;

<sup>1</sup>Inst. for Advanced Studies in Educ., CIAE-IE, Univ. of Chile, Santiago, Chile; <sup>2</sup>Pontifical Catholic Univ. of Chile, Santiago, Chile

**Abstract:** Cooperation is a complex human behavior that is fundamental to social functioning. Recent studies have shown that interbrain coupling emerges during dyadic cooperative interactions. However, it remains unclear whether such coupling reflects the joint execution of the task itself or serves as a marker of the underlying relational state that shapes how dyads engage with the task. Here, we demonstrate that interbrain coupling during cooperation is modulated by the level of mutual trust established prior to the task. The study included data from 140 healthy university students randomly assigned to 70 male-male dyads (mean age = 22.66 years, SE = 0.28, range = 18-35 years). In the first step, mutual trust was experimentally manipulated using an economic trust game, resulting in two groups of 35 dyads each: one with high mutual trust (MT) and another with high mutual distrust (MD). Next, we used EEG hyperscanning to simultaneously record the brain activity of dyad members as they performed the same visual cue-target task cooperatively. At the behavioral level, as expected, the MT group showed significantly greater accuracy in the cooperative task ( $M = 77.54\%$ ,  $SE = 1.331$ ) than the MD group ( $M = 69.37\%$ ,  $SE = 2.128$ ),  $F(1, 68) = 10.599$ ,  $p = .002$ ,  $\eta^2 = 0.135$ . In addition, response times were positively correlated between partners in the MT group ( $r = .711$ ,  $t = 5.808$ ,  $p = 1.84 \times 10^{-7}$ ), but not in the MD group ( $r = -.001$ ,  $t = -0.0078$ ,  $p = .993$ ). Notably, mutual trust significantly predicted accuracy in the cooperative task ( $\beta = 1.562$ ,  $t(68) = 2.088$ ,  $p = .040$ ). At the interbrain level, we observed enhanced interbrain coupling in the gamma band (31-40 Hz, from -200 ms to 200 ms after target stimulus onset) and the alpha band (9-12 Hz, from stimulus onset to 700 ms post-stimulus) in the MT group compared to the MD group (gamma:  $F(1, 68) = 7.662$ ,  $p = .007$ ,  $\eta^2 = 0.101$ ; alpha:  $F(1, 68) = 4.699$ ,  $p = .034$ ,  $\eta^2 = 0.065$ ). Furthermore, stronger interbrain coupling in the alpha band was significantly associated with faster dyadic reaction times ( $r(68) = -.308$ ,  $t = -2.669$ ,  $p = .009$ ). Finally, higher levels of mutual trust significantly predicted increased interbrain coupling in both the gamma ( $\beta = 0.060$ ,  $t(68) = 2.176$ ,  $p = .033$ ) and alpha ( $\beta = 0.238$ ,  $t(68) = 2.109$ ,  $p = .038$ ) bands. These findings highlight the critical role of mutual trust in shaping both behavioral performance and neural synchronization during cooperation, offering novel insights into the mechanisms underpinning successful social interaction and the dynamic interplay between affective states and joint action.

**Disclosures:** P. Barraza: None. E. Rodriguez: None.

**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.07/OO2

**Topic:** I.06. Social Cognition

**Support:** JST Moonshot R&D (Grant Number JPMJMS2013)

**Title:** Comparing Anime-Style and Realistic Avatars in Virtual Reality Communication: An fNIRS Hyperscanning study

**Authors:** \*K. IZUMISAWA, K. HIGO, S. SHIMADA;  
Meiji Univ., Kanagawa, Japan

**Abstract:** Avatars play a crucial role in shaping interpersonal communication within virtual reality (VR) environments. While previous studies have shown that an avatar's appearance can influence emotional recognition and social presence, it remains unclear how different avatar types affect neural synchronization between users—particularly in brain regions associated with theory of mind (ToM). This study investigated the impact of avatar appearance on interpersonal communication and inter-brain coupling in VR using a functional near-infrared spectroscopy (fNIRS) hyperscanning. Thirty-six participants were assigned to one of two groups: a realistic-style avatar group ( $M = 21.06$ ,  $SD = 1.65$ ) or an anime-style avatar group ( $M = 20.30$ ,  $SD = 1.66$ ). Pairs of participants engaged in a communication task involving five progressively self-disclosing questions while interacting through one of the two avatar types. The task comprised three phases: resting state, thinking time, and discussion. Brain activity was recorded throughout using fNIRS, focusing on 17 channels centered around the temporo-parietal junction (TPJ), a core region implicated in ToM processing. After the task, participants completed a questionnaire on their experience. Inter-subject correlation (ISC) analyses were conducted between corresponding channels of each participant pair. A two-way ANOVA with group (realistic vs. anime) and phase (resting vs. discussion) revealed significant interaction effects in channel pairs corresponding to the left superior parietal lobule ( $p = 0.02$ ) and the right supramarginal gyrus ( $p = 0.001$ ). In the realistic-avatar group, ISC during the discussion phase was significantly higher than during resting in the right supramarginal gyrus ( $p = 0.01$ ). In contrast, the anime-avatar group showed higher ISC in the left superior parietal lobule during discussion ( $p = 0.04$ ). These findings suggest that the realistic-style avatars may promote greater interpersonal attunement by engaging ToM-related processing in the right supramarginal gyrus, a region implicated in inferring others' thoughts and emotions. In contrast, the increased ISC in the left superior parietal lobule observed in the anime-style avatar group may reflect heightened engagement of self-related processing, possibly due to the stylized and less lifelike features of the avatars. Together, these results indicate that avatar appearance modulates the neural mechanisms underlying communication in VR, differentially recruiting social and cognitive processes.

**Disclosures:** K. Izumisawa: None. K. Higo: None. S. Shimada: None.

**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.08/OO3

**Topic:** I.06. Social Cognition

**Support:** NIH Grant R00MH120257  
NIH Grant 1F31MH138084-01  
NSF GRFP Award #2236868

**Title:** Within-individual neural patterns differ for memories of self- and other-generated interpretations of the same stimuli

**Authors:** \*C. SAVA-SEGAL<sup>1</sup>, T. BENSON<sup>2</sup>, E. FINN<sup>1</sup>;  
<sup>1</sup>Dartmouth Col., Hanover, NH; <sup>2</sup>Rutgers Univ., New Brunswick, NJ

**Abstract:** Ambiguous stimuli can be interpreted and remembered in multiple ways, making them ideal for studying subjective memory. Social contexts, such as considering others' opinions, often expose us to interpretations that differ from our own. Yet, how the *source* of an interpretation - i.e., self vs. other - shapes memory remains underexplored. We developed an fMRI encoding/recall paradigm using ambiguous images that elicit multiple interpretations. In session one, 54 participants generated their own interpretation (SELF) and were shown another person's interpretation (OTHER), selected in real-time based on semantic (dis)similarity to their own (SELF). Participants rated how much they liked each interpretation. In session two, a week later, they freely viewed each image again and were cued to recall both SELF and OTHER (order counterbalanced). Behaviorally, both interpretations were recalled above chance, though SELF was recalled more accurately. SELF and OTHER merged (i.e., became more similar than they were originally) in memory, but this merge was asymmetrical: OTHER shifted to resemble SELF more than vice versa ( $p < .001$ ). Neurally, we analyzed multivariate activity patterns in 100 cortical parcels and the hippocampi. Comparing SELF- vs. OTHER-cued viewings, we found that interpretation cues significantly shaped activity in many multimodal cortical regions, despite identical sensory input ( $q < .05$ , FDR corrected). Critically, trials with greater behavioral merging showed less distinct SELF/OTHER patterns in bilateral DLPFC, TPJ, and the left temporal pole. The asymmetry of merging—when OTHER shifted more than SELF—was also reflected neurally, particularly in TPJ and medial cingulate, and was modulated by how much participants had liked the OTHER interpretation in session 1. Together, these findings suggest that self-generated interpretations serve as a default anchor in memory, shaping how ambiguous experiences are encoded and recalled. They extend classic self-referential memory effects and egocentric biases in perspective-taking and recall, showing that memory biases for self over other extend to self-generated content, not just self-relevant information, and are reflected in neural representations.

**Disclosures:** C. Sava-Segal: None. T. Benson: None. E. Finn: None.

**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.09/OO4

**Topic:** I.06. Social Cognition

**Support:** NIDA Grant R01 DA051573

**Title:** Agency to choose social information enhances peer influence in adolescent risky decision-making

**Authors:** \*S. WANG<sup>1,2</sup>, J. M. WANG<sup>1</sup>, N. MELVILLE<sup>1</sup>, C. WANG<sup>1</sup>, M. A. ORLOFF<sup>3</sup>, D. CHUNG<sup>4</sup>, B. CASAS<sup>1,2</sup>, P. H. CHIU<sup>1,2</sup>;

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**Abstract:** Adolescence is a developmental period characterized increasing engagement in risky behaviors. While evidence suggests that peer influence contributes to the spread of risk-taking among adolescents, little attention has been paid to methods by which peer influence can be augmented or reduced. Given previous findings that information acquired under agency is perceived as more valuable, we examine in adolescents whether the impact of autonomously chosen social information (i.e., with agency) differs from passively provided social information on behavioral and neural metrics of peer influence. In this study, participants between 13-14 years of age completed a risky decision-making task, where they made choices between a safer and a riskier gamble, either after seeing the choices of two social peers or alone. We manipulated agency effect by letting participants decide which trials to view peers' choice ('Choice' condition), or randomly presenting peers' choice across trials ('No-choice' condition). Participants underwent functional magnetic resonance imaging in a 3T Siemens Prisma during the task. We adapted a behavioral economic utility model to assess the value of social information on risky choices (i.e., additional utility conferred to the specific gamble by viewing others choosing it) under each condition. Preliminary analysis showed that adolescents tended to follow peers' choices in both conditions. As expected, greater utility was conferred to the gambles chosen by social others in the Choice condition than in the No-choice condition, indicating an increased value of social information under agency. Furthermore, activation difference across conditions in ventromedial prefrontal cortex (vmPFC) when viewing peers' choices was correlated with condition difference of the value of social information. These results demonstrated that peer influence on risky choices is enhanced when adolescents have the agency to choose social information, and suggests enhanced vmPFC activity under agency underlie the enhanced peer influence.

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**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.10/OO5

**Topic:** I.06. Social Cognition

**Support:** JSPS KAKENHI Grant No. 24-K23879

**Title:** The effect of soft tactile perception on social distance and social memory.

**Authors:** \*T. TAKANO<sup>1</sup>, K. MOGI<sup>2</sup>;

<sup>1</sup>Univ. of Tokyo, Tokyo, Japan; <sup>2</sup>Sony Computer Sci. Labs., Shinagawa-Ku, Japan

**Abstract:** In recent years, while research on large language models (LLMs) have achieved remarkable progress, some researchers consider LLMs fall short of human abilities, especially in terms of embodied cognition. For example, holding a cup of hot coffee makes participants' impression of others better, suggesting physical warmth increases interpersonal warmth (Williams & Bargh, 2008). Some researchers have suggested that the process of building affectional bonds between infants and caregivers thorough physical contact, which is called attachment (Bowlby, 1969), underlies the embodied cognition of warmth (Fay & Maner, 2012; Inagaki et al., 2013). Harlow (1958) showed it important for the proper physical and mental development to get softness and warmth through touch in rhesus macaque infants. Social cognition is an important element of human intelligence. In human cognition, social memory, the ability to identify other people, plays an important role. Compared to the number of studies on implications of embodied cognition of warmth, few studies have investigated the effects of soft tactile perception on social cognition. However, given that touching a piece of a soft blanket promotes participants' tolerance for charity (McCabe & Nowlis, 2003) and that students sitting on fabric-covered benches in a classroom were more likely to engage in social interaction (Sommer & Olsen, 1980; Wong et al., 1992), it is possible that the softness can elicit participants' social behavior. Here we investigated whether soft tactile stimuli given to participants made them judge others as more compatible, finding it easier to recognize them. Participants were randomly assigned to either a soft or hard chair condition and asked to judge the social distance based on the degree of compatibility predicted from the faces shown on the screen (measuring distance task). One week after the measuring distance task, they were asked to participate in the facial recognition task. We also conducted these tasks in the same manner for objects instead of faces, in order to examine whether the soft tactile perception had an effect only on social context. Oxytocin, released through gentle touch (Matthiesen et al., 2001), changes social impressions of others (Ellingsen et al., 2014) and increases recognition memory (in mice, Takahashi et al., 2023). Taking into account the oxytocin released by soft tactile perception and the recognition memory led by oxytocin secretion, we hypothesize possible neural mechanisms of embodied cognition of softness and discuss the significance of softness in social context.

**Disclosures:** T. Takano: None. K. Mogi: None.

**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.11/OO6

**Topic:** I.06. Social Cognition

**Title:** Separate regions supporting language and social cognition in the anterior temporal lobe

**Authors:** A. AGARWAL, \*B. M. DEEN;  
Tulane Univ., New Orleans, LA

**Abstract:** The human anterior temporal lobe (ATL) is thought to play a critical role in both language and social cognition. Patients with ATL dysfunction resulting from brain damage or neurodegeneration can have difficulty naming objects or recognizing people, or can have dramatic social behavioral deficits as observed in Klüver-Bucy syndrome. Nevertheless, the detailed functional organization of the ATL remains poorly understood, in part because much of the region suffers from signal dropout in fMRI data. Whether the ATL contains distinct subregions involved in language and social cognitive processes, or a common area involved in both, remains debated. Here, we study responses to language and social cognitive tasks in a sample of  $N = 10$  human participants, using multi-echo fMRI to enhance signal quality from the ATL. We find separate responses to language and social cognition in multiple anatomical zones within the ATL, including the temporal pole, superior temporal gyrus, middle temporal gyrus, and inferior temporal gyrus. To determine how functional subregions of the ATL are situated within functional networks across the whole brain, resting-state networks were defined in individual participants using the multi-scale hierarchical Bayesian model algorithm. ATL subregions with preferential responses to language or social cognition tasks had increased functional connectivity to whole-brain networks with similar task preferences. These results indicate that the ATL contains a complex patchwork of functionally distinct subregions making separate contributions to language and social understanding, rather than a single integrative hub.

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**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.12/OO7

**Topic:** I.06. Social Cognition

**Title:** Audio-based expectations modulate face perception in the human brain: an intracranial iEEG study

**Authors:** \*H. JUNG<sup>1</sup>, H. JAIN<sup>3</sup>, W. HUANG<sup>4</sup>, A. MAJUMDAR<sup>5</sup>, J. YIH<sup>6</sup>, C. PERRY<sup>7</sup>, L. GWILLIAMS<sup>2</sup>, J. PARVIZI<sup>4</sup>;

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**Abstract:** Across diverse fields of neuroscience, extensive evidence suggests that expectations significantly shape perception. Yet, the neural mechanisms, especially in cross-modal settings, remain elusive. Leveraging the anatomical precision and high signal-to-noise ratio of intracranial EEG (iEEG), we investigate how auditory narratives describing an upcoming face modulate its subsequent visual perception. Our multimodal approach, in conjunction with deep neural networks to construct rich auditory and visual embeddings, offers insights into the neural mechanism of cross-modal expectations.

Twenty-one participants (N=20, after one removal for low cognitive function) listened to short audio clips describing a face's characteristics ("audio"), then viewed and rated the face ("face"). All participants provided informed consent; study protocol was approved by Stanford University's IRB.

iEEG High-Frequency Band (HFB) signals were preprocessed and epoched. To quantify the perceptual and semantic content of the stimuli, we utilize three types of embeddings: 1) low-level auditory (melspectrogram) capturing acoustic properties, 2) high-level language (GPT-2 from transcripts), reflecting broader context and abstracted semantic meaning, and 3) Face (OpenAI CLIP) capturing visual to semantic content. A 5-fold cross validated ridge regression with a sliding window predicted the time-varying HFB brain signals with the face perception epoch using these embeddings.

Results first confirmed face-selective HFB activity in canonical face active regions (fusiform gyrus and collateral sulcus) and auditory-selective activity in audio-active regions (superior temporal gyrus, lingual gyrus). Within these auditory-active regions, both low- and high-level language embeddings significantly predicted HFB variance during the auditory epoch.

Importantly, auditory embeddings from the predictive narratives significantly predicted neural activity within the face-active fusiform gyrus during subsequent face perception. Such findings provide iEEG evidence that auditory-driven expectations are actively reflected in and drive visual processing, dynamically modulated face perception.

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## **Poster**

### **PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.13/OO8

**Topic:** I.06. Social Cognition

**Title:** Naturalistic "dark matter": shared signals of information processing persist after removing stimulus-computable features

**Authors:** \***T. L. BOTCH**<sup>1</sup>, H. SONG<sup>2</sup>, T. VANDERWAL<sup>3</sup>, M. D. ROSENBERG<sup>4</sup>, E. S. FINN<sup>1</sup>;

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**Abstract:** Everyday experience is composed of rich, multimodal information. Traditionally, cognitive neuroscientists have aimed to understand how the brain represents and processes this information using controlled stimuli and tasks targeting specific sensory features and/or cognitive functions. While this approach has yielded substantial insight into the neural architecture supporting cognition, these designs decontextualize both sensory features and neural processing from the complexity of the natural world. In turn, they assume, explicitly or implicitly, that neural representations of real-world information are built from the sum of their parts. Here, we question the validity of this assumption by directly evaluating the ability to model shared, stimulus-driven signals observed during naturalistic processing (i.e., movies, auditory stories) and traditional task paradigms (i.e., N-back, emotion recognition). We leveraged three large functional MRI (fMRI) datasets where subjects listened to either auditory stories or watched audiovisual movies (Narratives, Nastase et al., 2021; TheMoth, Lebel et al., 2021; AVID, Sava-Segal et al., 2023). We also used two datasets where subjects completed both naturalistic and traditional task paradigms (HCP7T, Van Essen et al., 2013; IBC, Pinho et al., 2018). We first isolated shared, stimulus-driven signals for each by calculating the inter-subject correlation (ISC) for each subject and stimulus (Hasson et al., 2004). Within both naturalistic and task paradigms, we observed high ISC within unimodal cortices (i.e., early visual / auditory) that gradually declined when moving into higher-order cognitive regions (i.e., language, theory of mind). We then extracted hypothesized features (e.g., luminance, loudness) and artificial neural network activations for each stimulus and used these features as predictors of brain activity. Following model fitting, we extracted the residual time series (the unmodeled signal) for each subject and used this time series to calculate ISC (“residual ISC”). While these stimulus-computable features captured some explainable variance in brain activity, significant ISC remained across cortex and the ability to model these shared responses declined moving from unimodal to heteromodal cortex. Critically, we found that significantly more signal was explained within task paradigms (average 19%) compared to naturalistic paradigms (average 10.5%). Together, this indicates that ISC, particularly within heteromodal cortex, is greater than the sum of its modelable parts and may carry emergent features of cognitive representation within naturalistic contexts.

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**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

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**Topic:** I.06. Social Cognition

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Singularity Professor Research Project of KAIST  
Korea Institute of Science and Technology (KIST)'s Institutional Research Project (2E33701)  
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**Title:** Spontaneous social tipping and trend cycles driven by randomness

**Authors:** \*H. LEE<sup>1,3</sup>, S. BAEK<sup>1</sup>, J. JANG<sup>3</sup>, S.-B. PAIK<sup>1,2</sup>;

<sup>1</sup>Dept. of Bio and Brain Engin., <sup>2</sup>Dept. of Brain and Cognitive Sci., KAIST, Daejeon, Korea, Republic of; <sup>3</sup>Ctr. for Brain Convergence Research, Brain Sci. Inst., KIST, Seoul, Korea, Republic of

**Abstract:** Conventional theories and human behavioral experiments suggest that the emergence of new social conventions requires a minority group reaching a critical mass (Centola, 2018). These findings rest on two key assumptions: (1) the presence of fixed innovators who consistently introduce new behaviors, and (2) that all others engage in conformist imitation — copying the majority behavior. Here, we propose a fundamentally different framework for understanding social change. In our model, social conventions can shift spontaneously without any critical mass of committed individuals. This is driven by random imitation, where individuals copy others in proportion to the frequency of observed behaviors, rather than conforming to the majority. Furthermore, instead of fixed innovators, we assume the presence of random innovators, who adopt new behaviors stochastically. Our results demonstrate that social tipping can emerge without any dependence on a critical mass within the population. Remarkably, our model shows that the entire population can shift to a new behavioral state even when no individual starts by performing the new behavior. Unlike previous models, our framework reveals a novel dynamic in which the system exhibits spontaneous trend cycles, where dominant behaviors are periodically replaced by new ones over time. These dynamics are analytically tractable via a simple Markov chain-based mathematical model. Together, our findings demonstrate how individual-level randomness—in both imitation and innovation—can drive tipping points and cyclical changes in social conventions without requiring committed minorities, offering new insights into the neural and behavioral mechanisms of collective dynamics.

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**Program #/Poster #:** PSTR243.15/OO10

**Topic:** I.06. Social Cognition

**Support:** NRF-2022R1A2C3008991  
Singularity Professor Research Project of KAIST

**Title:** Payoff-independent random imitation as a mechanism of cultural evolution

**Authors:** \*S. BAEK<sup>1,2</sup>, H. LEE<sup>4,2</sup>, A. ZHENG<sup>3</sup>, J. JANG<sup>4</sup>, S.-B. PAIK<sup>2,3</sup>;  
<sup>2</sup>Dept. of Bio and Brain Engin., <sup>3</sup>Dept. of Brain and Cognitive Sci., <sup>1</sup>KAIST, Daejeon, Korea, Republic of; <sup>4</sup>Ctr. for Brain Convergence Res., KIST, Seoul, Korea, Republic of

**Abstract:** Cultural evolution refers to the transmission and accumulation of non-genetic information—such as behaviors, skills, and norms—across generations in human and animal societies (Richerson, 2008). Traditionally, this process has been understood through the lens of payoff- or success-biased imitation (Bridges, 2024), aligning with Darwinian models in biological evolution that emphasize selection-based copying (Mesoudi, 2009). However, observations from diverse real-world contexts show that unbiased, payoff-irrelevant imitation is common (Bentley et al., 2004), questioning the necessity of strategic selection in cultural evolution. In this study, integrating data from animal behavior observations, controlled human psychophysics experiments, and computational model simulations, we propose a fundamentally different view of cultural evolution that unbiased random imitation alone can drive adaptive cultural dynamics in the absence of payoff-based selection. First, behavioral analysis of a non-human primate group learning a novel foraging task revealed that individuals demonstrating the greatest payoff improvements had initially engaged predominantly in random, payoff-irrelevant imitation. Next, in a controlled human psychophysics experiment, participants consistently exhibited frequency-based random imitation in early stages, prior to fully learning any payoff contingencies through repeated exposure. To understand the effects and mechanisms underlying these observed behavioral patterns, we conducted computational simulations using a multi-agent evolutionary model. Each agent was employed various strategies — payoff-biased imitation, unbiased random copying, or pure trial-and-error behavior — and was evaluated how effectively it could collect or consume resources. Contrary to conventional expectations, under realistic environmental uncertainty, agents relying on random imitation alone showed significantly more efficient convergence toward optimal behavioral traits than those using selective imitation, which frequently led to suboptimal plateaus. These findings challenge the view that strategic selection is essential, highlighting random imitation as a key adaptive mechanism driving cultural evolution.

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**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

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**Topic:** I.06. Social Cognition

**Support:** NRF-2022R1A2C3008991  
Singularity Professor Research Project of KAIST

**Title:** Frequency-based imitation as a core heuristic in human learning

**Authors:** \*A. ZHENG<sup>1,2</sup>, S. BAEK<sup>3</sup>, H. LEE<sup>4</sup>, J. JANG<sup>4</sup>, S.-B. PAIK<sup>2,3,1</sup>;

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<sup>4</sup>Ctr. for Brain Convergence Res., Brain Sci. Inst. Korea Inst. of Sci. and Technol., Seoul 02792, Korea, Republic of

**Abstract:** Learning is widely assumed to rely on outcome-based feedback. However, in real-world settings, feedback is often ambiguous or incomplete. What learning mechanisms support behavior in such uncertain environments? We propose that humans, as inherently social creatures, can learn by observing others—even when explicit feedback is lacking. More specifically, we investigate frequency-based imitation: the tendency to adopt behaviors simply because they are more commonly seen in others, regardless of their actual effectiveness or reward. While earlier research has documented this bias in contexts lacking reward differences in outcomes, our study is the first to show that such imitation also emerges when certain choices offer greater rewards than others. To examine this, we conducted a behavioral experiment in which participants selected among visual stimuli associated with varying probabilities of reward, aiming to identify high-reward options and maximize their gains. Before making each decision, participants observed choices made by artificial agents, with some options chosen more frequently than others. Importantly, the agents' choice frequencies bore no relation to reward values. The findings revealed that participants gradually acquired reward knowledge, as evidenced by increased preference for high-reward stimuli over time. At the same time, they consistently favored options frequently chosen by agents—even when these did not confer any reward advantage—indicating a robust frequency bias independent of outcome awareness. Moreover, participants showed the strongest preference for options that were both frequently chosen by agents and highly rewarding, suggesting that frequency-based and reward-driven learning can coexist. Collectively, these results demonstrate that frequency-based imitation is not just a fallback under uncertainty, but a robust and persistent feature of human learning. We argue that it serves as a core heuristic that shapes learning in feedback-limited, real-world environments.

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**Program #/Poster #:** PSTR243.17/OO12

**Topic:** I.06. Social Cognition

**Support:** NRF-2022R1A2C3008991  
Singularity Professor Research Project of KAIST

**Title:** Stochasticity and Imitative Strategy in Multi-agent Optimization

**Authors:** \*Y. SEO<sup>1,2</sup>, S. BAEK<sup>3</sup>, S.-B. PAIK<sup>2,3</sup>;

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**Abstract:** Reinforcement learning (RL) has achieved outstanding results in real-world situations. Nevertheless, its success is confined to single-agent scenario, which cannot be solved efficiently in multi-agent system. In multi-agent system, limited resources and environment dynamics often cause competition among agents and disrupts global system optimization. To address this, prior works in multi-agent deep reinforcement learning (MADRL) have employed mechanisms like real-time state sharing and adaptive policy updates. Despite their promise, such mechanisms frequently struggle with scalability in complex environments due to their computational demands and the inherent instability caused by multiple learning agents. Intriguingly, social animal's behavior in nature suggests that decentralized coordination can emerge from simple mechanisms like stochastic exploration and imitation. Inspired by this, we introduce a hybrid coordination framework that integrates stochastic and imitative strategies to mitigate competitive dynamics in multi-agent systems. We validated our approach in a multi-agent traffic simulation where all agents aim to reach a shared destination. As the scale of the multi-agent system increases, congestion becomes more severe when all agents adhere to globally optimal path. To alleviate this, we first deploy a subset of innovator agents, who stochastically deviate from the optimal path to explore alternative routes. While stochastic behavior effectively mitigated congestion, the optimal number of innovators depended on the system scale. To further improve adaptability in the face of non-stationary environment, we added imitator agents, who mimic the actions of preceding agents. Markedly, this action copying mechanism enhanced coordination and further improved traffic throughput. In addition, our simulation reveals that the optimal configuration involves a small fraction of innovators and a majority of imitators, resulting in emergent decentralized coordination without explicit communication. These findings provide a potential approach to addressing challenges in multi-agent systems that cannot be resolved solely through single agent models.

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**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

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**Program #/Poster #:** PSTR243.18/OO13

**Topic:** I.06. Social Cognition

**Title:** Modeling the Exchange of Gut Microbiota in a Social Network\_Agent-Based-Model Analysis of the Influence of Social Hubs.

**Authors:** \*M. ISHII;

The Univ. of Tokyo, Kamakura, Japan

**Abstract:** Momoka Ishii and Ken Mogi

The gut microbiota has emerged as a pivotal factor in human health, behavior, and mental life (Cryan & O'Mahony 2011). Although many studies have linked individual bacterial strains to specific outcomes, very few have actually quantified how entire microbial communities migrate between people by daily contact, and even fewer have integrated microbiota analysis of social-interaction. We constructed and analyzed an Agent-Based Model (ABM) (An et al. 2017) that simulated 100 to 150 individuals exchanging gut bacteria across a small social network, in which we asked three core questions: 1) The effect of social contact on within-host diversity, quantified by the Shannon index (Shannon 1948), and inter-host  $\beta$ -diversity, quantified by cosine distance. 2) The nature of functional overlap, defined as cosine similarities among KEGG metabolic vectors (Kanehisa et al. 2017). 3) The quantitative role of people at social hubs, in amplifying community-wide microbial change (Brito et al. 2019). In the simulation, each agent began with a twenty-strain gut profile. Ten strains were well-characterized human symbionts retrieved through the KEGG API (Kanehisa et al. 2017). Ten additional dummy strains were synthesized to create a controlled gradient of pathway overlap. We constructed KEGG pathways and stored their pairwise cosine similarities as a  $20 \times 20$  weight matrix. Every agent initiated one stochastic interaction with a neighbor with a range of exchange probabilities. When exchange took place, it was assumed that the donor exported its top  $N = 5$  most abundant strains, each carrying a transmission weight equal to its abundance multiplied by its metabolic-overlap score relative to the receiver's incumbents. The receiver blended newcomers by weighted averaging, with the total population normalized to unity. The simulation suggested that  $\beta$ -diversity contracted network-wide, yet the contraction was fastest inside hub-centered subgraphs. While the Shannon diversity of socially central agents increased, their cosine distance to other members decreased, suggesting that various bacterial exchange steps elevated diversity, simultaneously reducing similarity to individual agents by increasing representations within the group.

**Disclosures:** M. ishii: None.

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**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.19/OO14

**Topic:** I.06. Social Cognition

**Support:** Swiss Epilepsy Foundation

**Title:** Context dependent encoding of contextual variables in human temporal lobe

**Authors:** A. KISELEVA<sup>1</sup>, J. SARNTHEIN<sup>2</sup>, H. JOKEIT<sup>1</sup>, L. IMBACH<sup>1</sup>, T. DUBCEK<sup>1</sup>, \***D. LEDERGERBER**<sup>3</sup>;

<sup>1</sup>Swiss Epilepsy Center, Clin. Lengg, Zurich, Switzerland; <sup>2</sup>Klinik für Neurochirurgie, Universitätsspital Zurich, Zurich, Switzerland; <sup>3</sup>Swiss Epilepsy Center, Klinik Lengg AG, Zürich, Switzerland

**Abstract:** When encoding an episodic memory trace of a situation, contextual information of the situation is highly relevant for separating this memory trace from instances of similar happenings at different times or in different contexts. Neurons in the rodent medial temporal lobe that show stable fields of activity in places of the environment (place cells) or in goal locations (goal cells) show modulation of firing rate depending on task conditions or timing elements. In contrast, a recent report showed that concept neurons in human medial temporal lobe (MTL) do not appear to be modulated by such contextual information. We thus investigated, whether human MTL utilizes an alternative mechanism for encoding contextual information. Epilepsy patients with intracranial electrodes for seizure monitoring passively watched a film in which emotionally charged and neutral clips alternated, while, in both trial types, the main object underwent continuous changes in size and speed. From these recordings, we isolated 500 neurons from 19 patients and applied a Generalized Linear Model (GLM) selection procedure to find whether their firing rate was modulated by one or more of the three covariates: trial type, size of the dominant object, and its movement across frames. We found the highest number of neurons encoding the difference between trials of landscapes versus emotional faces (14%). A smaller but substantial population of neurons showed specificity for the main object's size and degree of movement (5% and 6%, respectively). Additionally, 3% of neurons demonstrated mixed selectivity, responding to the combination of at least two visual features. Neurons with different specificity were relatively equally distributed across MTL regions. When splitting the data between neutral and emotionally charged trials, we found that many neurons changed their specificity according to trial type. Additionally, the proportions of neurons with object speed and size modulation were affected by trial type. Overall, this suggests that a population of neurons distributed across all MTL regions encodes the contextual features of situations passively observed by patients. These neurons' specificity additionally show adaptation to the emotional content of the trials.

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**Topic:** I.06. Social Cognition

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**Title:** Hippocampal Map-like Representations of Social Recognition Dimensions

**Authors:** \*W. KANG<sup>1,2</sup>, M. KWON<sup>1,3</sup>, S.-H. LEE<sup>1,2,3</sup>;

<sup>1</sup>Dept. of Psychology, Col. of Social Sci., <sup>2</sup>Neurosci. Res. Institute, Med. Res. Ctr., <sup>3</sup>Inst. of Psychological Sciences, Inst. of Social Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

**Abstract:** The ability to recognize social relationships is essential to understanding and interacting within complex social environments. Our previous research identified two principal dimensions underlying interpersonal relationship recognition: the first dimension (PC1) reflects Amity-Hostility, and the second dimension (PC2) captures Restrained Amity-Suppressive Hostility. These dimensions are processed in distinct cortical regions, with PC1 primarily encoded in the right posterior superior temporal sulcus (rpSTS) and PC2 predominantly represented in the right ventromedial prefrontal cortex (rvmPFC). However, how the brain integrates these dimensions into a unified representation of interpersonal relationships remains unclear. Here, we investigated whether the hippocampus encodes social relational information within a two-dimensional space defined by PC1 and PC2 dimensions, analogous to spatial mapping. To address this, we conducted an event-related functional magnetic resonance imaging (fMRI) experiment. During the experiment, participants viewed naturalistic movie clips and assessed the social relationship between a designated actor and target character. Using representational similarity analysis (RSA) and support vector regression (SVR), we observed that the hippocampus represents interpersonal relationships based on distances in the PC1-PC2 space. In contrast, the rpSTS and rvmPFC selectively encoded dimension-specific information corresponding to the PC1 and PC2 dimensions, respectively. Mediation analysis showed that hippocampal representations reflect distinct contributions of the rpSTS and rvmPFC. Feature transfer analysis further confirmed that the hippocampus receives dimension-specific information from these cortical areas, demonstrating a unidirectional flow of information from cortex to hippocampus, with no evidence of significant reverse transfer. Collectively, these findings suggest that the hippocampus integrates dimension-specific cortical inputs into a unified, map-like representation of interpersonal relationships.

**Disclosures:** W. Kang: None. M. Kwon: None. S. Lee: None.

**Poster**

**PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.21/OO16

**Topic:** I.06. Social Cognition

**Support:** RS-2024-00348130  
RS-2025-02304581  
IBS-R015-D1  
S-2023-0794-000  
H19C1328

**Title:** Hierarchical processing of social interactions in naturalistic conversations

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**Abstract:** Understanding others' social interactions is essential for navigating dynamic social environments. While prior research has emphasized the lateral visual stream in social information processing, how the brain extracts multilayered social information from verbal conversation remains largely unexplored in naturalistic settings, despite its central role in daily communication. To examine the hierarchical processing of dyadic social interactions, participants watched movies in the scanner (3T, 3 mm iso, N = 41) featuring two former romantic partners seated at a table and engaged in emotionally rich, socially dynamic conversation in a consistent setting. This natural conversation within a stable environment enabled modeling of reciprocal dialogue while minimizing extraneous factors such as scene changes or interruptions from other characters. Auditory and semantic features were extracted from the characters' utterances via the sound envelope and sentence embeddings generated by a Korean BERT model respectively. Higher-level social and affective features were derived from participant ratings and descriptive annotations. To model social interaction patterns, two independent participant groups (N = 14, 12) rated each character's intention toward the other on an avoid-approach continuum. These ratings defined a two-dimensional interaction space with one axis reflecting a character's intention in the current scene and the other representing the partner's response in the subsequent scene. This space captured distinct social dynamics such as mismatched (rejected vs. pursued) or aligned (mutual interest vs. disinterest) intentions, forming the basis for our social interaction features. For affective features, an independent annotator provided nuanced, context-rich action terms (e.g., blaming, caring) for each social exchange, which were semantically embedded. A banded ridge regression model estimated the unique variance in brain responses explained by each feature space. We observed a gradient along the lateral temporal cortex: auditory features in primary auditory cortex (A1), semantic features in superior temporal gyrus (STG), and social features in superior temporal sulcus (STS). Anterior STS and ventromedial prefrontal cortex (vmPFC) were additionally engaged in processing the affective features of social actions during movie viewing. These findings suggest that representations of dyadic social interactions are abstracted and contextualized by social dynamics along a superior-to-inferior gradient in the lateral temporal cortex, progressing from sensory to social processing.

**Disclosures:** J. Ro: None. L. Chang: None. W. Shim: None.

**Poster**



## **PSTR243: Human Social Cognition: Behavioral and Neural Processes II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR243.22/OO17

**Topic:** I.06. Social Cognition

**Support:** National Science and Technology Council (STC 113-2628-H-002-004-)  
Ministry of Education (MOE) NTU-113V2013-1  
National Science and Technology Council (113-2410-H-002 -219 -MY3)

**Title:** Unraveling the roles of prefrontal and posterior cingulate cortices in belief updating on a controversial issue

**Authors:** \*P. F. CHIEN<sup>1</sup>, P.-J. B. HSIEH<sup>2</sup>;

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**Abstract:** Belief polarization on political and socio-scientific issues is increasingly pervasive. Although previous research has identified the roles of information content, personality traits, and metacognitive abilities in shaping belief formation and stability across polarized groups, the neural mechanisms supporting the dynamic integration of opposing or supportive viewpoints on societally consequential topics remain unknown. Here, we investigate the neural and cognitive dynamics of belief updating by presenting participants with naturalistic video segments offering either critical or affirmative perspectives on a controversial socio-scientific issue, with the order of presentation systematically counterbalanced. Participants provided agreement ratings before and after each video and completed a standardized measure of intolerance of uncertainty to quantify individual differences in ambiguity tolerance. We demonstrate that exposure to both critical and affirmative perspectives reliably shifts beliefs, with the magnitude and direction of these shifts strongly modulated by the order in which information is presented. Functional MRI data analyzed via inter-subject representational similarity analysis (IS-RSA) reveal that belief updating consistently engages a core neural network encompassing the dorsomedial prefrontal cortex (DMPFC), posterior cingulate cortex/angular gyrus (PCC/AG), anterior cingulate cortex (ACC), precentral gyrus, and insula. Crucially, participants exhibiting greater belief change show increased neural pattern similarity shifts in the anterior ventrolateral prefrontal cortex (VLPFC), implicating this region in the active integration of new evidence into existing cognitive schemas. Furthermore, opposing perspectives selectively enhance temporal correlations in the ventromedial prefrontal cortex (VMPFC), caudate, and PCC, whereas supportive viewpoints preferentially recruit the caudate and frontal eye fields. Together, these findings delineate a flexible and context-sensitive neural architecture underlying belief revision. By identifying the prefrontal cortex and PCC as critical hubs for epistemic information integration, this study provides a mechanistic account of open-minded information processing and lays the foundation for interventions aimed at reducing societal polarization and fostering constructive public discourse.

**Disclosures:** P.F. Chien: None. P.B. Hsieh: None.

## **Poster**

### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR244.01/OO18

**Topic:** I.08. Learning and Memory

**Support:** NIH BRAIN Initiative grant U19NS104590

**Title:** Hippocampal neural ensemble representations underlying the use of an abstract rule

**Authors:** \*A. TSAO<sup>1,2</sup>, M. J. SCHNITZER<sup>1,2,3,4,5</sup>;

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**Abstract:** Abstraction is central to cognition. However, the way in which neural representations of abstractions form during learning and are used in new circumstances is poorly understood. We examined neural population representations of a basic abstract rule by tracking over weeks the coding properties of hippocampal neurons in rats acquiring and applying knowledge about a learning set task. This task comprised a series of problems, each conducted on a continuous T-maze and using a novel pair of unique odors. On each trial, one of the two odors was presented, indicating whether the rat should turn left or right to receive a reward. This task has a simple abstract structure that allows one-shot learning for new problems; the initial trial of each problem reveals the mapping between odors and rewarded turning directions. Rats trained on tens of problems learnt to use the abstract structure and achieve one-shot learning. To examine the basis for the rats' acquisition of the abstract rule, we used a head-mounted mini-microscope for time-lapse imaging of the calcium dynamics of large sets of CA1 pyramidal cells as rats acquired and applied knowledge of the task's abstract structure. Analyses revealed three subpopulations of cells with coding properties that generalized across problems: odor-responsive cells with dynamics that differentiated between rightward- and leftward-indicating odors; odor-responsive cells with activity that differentiated between the odors presented first and those presented second at the start of a new problem; cells with place fields on the central stem of the maze and activity rates indicating the rat's upcoming turning direction. There was also a subpopulation of odor-responsive cells that responded with long latencies after odor presentation but that differentiated between odors only for a single problem. This subpopulation emerged late in acquisition of the learning set task, as the rats began to perform one-shot learning. The activity of this subpopulation was predictive of task performance, suggesting it served to temporally link the dynamics of abstract odor-coding cells to those of choice-coding cells in a problem-specific way. At the start of new problems, each of these subpopulations arose in a consistent order as rats began to perform one-shot learning. Across the entire course of learning, the sequence in which each abstract subpopulation emerged followed a clear stereotypical pattern across rats, whereas the development of coding properties for individual cells within each subpopulation followed less consistent patterns. Overall, our results show how the hippocampus may support the encoding and use of cognitive abstractions.

**Disclosures:** A. Tsao: None. M.J. Schnitzer: Other; MJS was a co-founder of Inscopix Inc, the manufacturer of the miniature integrated microscope; however, this financial interest was fully removed partway through our study..

## Poster

### PSTR244: Hippocampal Circuits

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR244.02/PP1

**Topic:** I.08. Learning and Memory

**Support:** DARPA W911NF2420108

**Title:** Optical imaging of interneuron activity in the mouse hippocampus

**Authors:** \*Y. R. WANG<sup>1</sup>, C. C. CHU<sup>1</sup>, M. DAVIES<sup>2</sup>, E. J. BERTACCINI<sup>4</sup>, B. MACIVER<sup>3</sup>, R. A. PEARCE<sup>1</sup>;

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**Abstract:** Amnesia is one of the key clinical endpoints of general anesthesia (GA), but the mechanism by which GA suppresses memory remains unclear.  $\gamma$ -Aminobutyric acid type A receptors incorporating  $\alpha 5$  subunits ( $\alpha 5$ -GABA<sub>A</sub>Rs) are highly expressed in the hippocampus and have been implicated in the suppression of learning and memory by etomidate. Counterintuitively, mice lacking  $\alpha 5$ -GABA<sub>A</sub>Rs in interneurons resist the amnestic effect of etomidate (M. Zhu et al., PNAS Nexus 2023). Transcriptomic analysis (Allen Institute database) indicates that the highest level of  $\alpha 5$ -GABA<sub>A</sub>Rs mRNA expression is in interneurons classified as Lysosomal Associated Membrane Protein 5-expressing (Lamp5-INs). To dissect the role of Lamp5-INs, we aim to develop optical imaging methods to examine their activity and output directly. Toward this end, we conducted *in vitro* calcium imaging in the hippocampal CA1 region, in brain slices from Lamp5-Cre mice injected with a Cre-dependent genetically encoded calcium indicator (GCaMP6s/8m), using a two-photon (2P) microscope (Bruker Ultima-2P+). We observed individual processes with a diameter of  $\sim 1$ -2 $\mu$ m connected to series of swellings matching the pattern of neurogliaform-family cells, which constitute Lamp5-INs in the hippocampus. These processes could be activated reliably by local electrical stimuli. They also underwent occasional spontaneous activation, the rate of which was significantly elevated following infusion of the  $\alpha 1$  adrenergic receptor ( $\alpha 1$ -AR) agonist A-61603, confirming that they arise from interneurons that express  $\alpha 1$ -ARs. The electrically induced response could be observed up to 400  $\mu$ m away from the stimulus source. In addition to recording neuronal activities directly by Ca<sup>2+</sup> imaging, we measured interneuronal output by imaging the GABA sensor GABASnFR2 in WT mice, using both 2P and widefield microscopy. Using a widefield microscope (4x objective), GABA release was detected across *stratum radiatum* (SR) and *stratum oriens* (SO) following electrical stimulation of SR. Application of the  $\alpha$ -Amino-3-

hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX) caused GABA release to be confined to SR. Using 2P microscopy, individual processes were not observed, but fluorescence in the full field was observed following local electrical stimulation. As with widefield microscopy, the signal was significantly reduced ( $46 \pm 2\%$ ) following CNQX infusion. We conclude that imaging axon terminals and extracellular GABA will enable us to distinguish between presynaptic modulation of GABA release versus alteration of disinhibition through interneuronal  $\alpha 5$ -GABA<sub>A</sub>Rs.

**Disclosures:** Y.R. Wang: None. C.C. Chu: None. M. Davies: None. E.J. Bertaccini: None. B. MacIver: None. R.A. Pearce: None.

## **Poster**

### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR244.03/PP2

**Topic:** I.08. Learning and Memory

**Support:** DARPA W911NF2420108

**Title:** Interneuronal  $\alpha 5$ -GABA<sub>A</sub>Rs contribute to optogenetically induced population spike suppression in the mouse CA1 hippocampus

**Authors:** \*C. C. CHU<sup>1</sup>, Y. R. WANG<sup>1</sup>, M. DAVIES<sup>2</sup>, E. J. BERTACCINI<sup>4</sup>, B. MACIVER<sup>3</sup>, R. A. PEARCE<sup>1</sup>;

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**Abstract:**  $\gamma$ -Aminobutyric acid type A receptors that incorporate  $\alpha 5$  subunits ( $\alpha 5$ -GABA<sub>A</sub>Rs) play a crucial role in the regulation of learning and memory. They are primarily found in pyramidal cells (PCs) but they are also present in some interneurons (INs) in the hippocampus. We recently reported that selective eliminating  $\alpha 5$ -GABA<sub>A</sub>Rs from INs prevents etomidate-induced contextual memory suppression, (M. Zhu et al., PNAS Nexus, 2023) indicating that interneuronal  $\alpha 5$ -GABA<sub>A</sub>Rs are essential pharmacologic targets for this end point. To determine how interneuronal  $\alpha 5$ -GABA<sub>A</sub>Rs modulate the responses of CA1 pyramidal neurons to Schaffer Collateral (SC) input, we measured extracellularly recorded population (PS) responses in hippocampal brain slices from wild-type and  $\alpha 5$ -IN-KO animals (Gad2-Cre; Gabra5-floxed). We activated interneurons optogenetically by injecting pAAV-mDlx-ChR2-mCherry-Fishell-3 (AAV9) into the dorsal hippocampus three weeks before harvesting brain slices. Light activation suppressed the PS at short interstimulus intervals (ISI), defined at the time between the onset of the light and the electrical stimuli, and augmented the PS at later intervals, with the duration of the light pulse determining the degree of PS suppression. The shortest light pulses (0.2-2 ms) suppressed the PS at ISIs up to 40 ms, intermediate pulses (1-5 ms) at ISIs up to 80 ms, and

longer pulses (5-10 ms) up to 160 ms. Etomidate (3.2  $\mu$ M) enhanced the suppression at short ISIs and reduced augmentation at longer ISIs. In mice lacking interneuronal  $\alpha$ 5-GABA<sub>A</sub>Rs, PS suppression was not different than in WT, and the etomidate effect was unaltered for short ISIs (10, 20, 40 ms), and at all intervals for light pulses of short and intermediate durations. However, for long light pulses and long ISIs (80, 160, 320, 640 ms), etomidate was less effective at suppressing the PS (LMEM, interaction between genotype and drug  $p < 0.001$ ). These results indicate that interneuronal  $\alpha$ 5-GABA<sub>A</sub>Rs either enhance GABAergic responses directly through a facilitatory presynaptic effect, similar to that reported recently in spinal cord (K. Hari et al., Nature Neurosci 2022), or indirectly through a disinhibitory pathway. The very long duration of the optogenetic response suggested that GABA<sub>B</sub>-receptors might be contributing to PS suppression and augmentation. Consistent with this possibility, the GABA<sub>B</sub> antagonist CGP55845 reduced PS suppression at 80 ms and reduced augmentation at later intervals (320, 640, 1280 ms).

**Disclosures:** C.C. Chu: None. Y.R. Wang: None. M. Davies: None. E.J. Bertaccini: None. B. MacIver: None. R.A. Pearce: None.

## **Poster**

### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR244.04/PP3

**Topic:** I.08. Learning and Memory

**Support:** R00MH129565  
Whitehall Foundation Research Grant  
Alfred P. Sloan Neuroscience Award  
Klingenstein Fellowship Award in Neuroscience

**Title:** Structured CA1 output motifs boost memory signal propagation during hippocampal reactivation

**Authors:** \*B. KANG<sup>1</sup>, S. QIU<sup>1</sup>, J. JEONG<sup>1</sup>, K. STACHOWICZ<sup>2</sup>, T. GEILLER<sup>1</sup>;  
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**Abstract:** Memory consolidation relies on the transmission of hippocampal activity to downstream brain regions via replay events that occur during sleep and quiet wakefulness accompanied by sharp-wave ripples (SWRs). While the content of these reactivations is well characterized, it remains unclear whether hippocampal output is diffusely broadcasted or routed through defined circuit motifs that enhance transmission efficiency. Here, we combined single-cell electroporation, monosynaptic tracing, and two-photon calcium imaging in behaving mice to identify and track CA1 hippocampal neurons that project to shared postsynaptic targets in the subiculum (SUB). Following a spatial learning task, we found that CA1 neurons with convergent

projections onto the same SUB neuron displayed enhanced, coordinated reactivation during “private” SWR; events where their co-activity exceeded that of randomly selected neurons. We further found that the strength of SUB recruitment during SWRs is modulated by the number of shared presynaptic inputs and the fraction of private SWRs post learning. We then used a spiking network model that to confirm the computational advantage of such motif, whereby SUB neurons are more likely to be activated during SWRs when they receive converging input from co-reactivated CA1 neurons. Then, we developed a mesoscale two-photon imaging approach to record activity from thousands of CA1 and SUB neurons simultaneously and used it to validate that CA1 ensembles with greater co-activity were more likely to share downstream targets in SUB. Finally, using all-optical manipulation, we selectively reactivated CA1 ensembles with holographic optogenetics and showed that stimulating neurons with shared SUB targets elicited stronger SUB responses compared to random activation of CA1 cells. Together, these findings challenge the notion that hippocampal replay is diffusely broadcasted. Instead, they reveal an anatomically structured circuit motif through which memory-related activity is selectively routed out of CA1 for consolidation.

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## **Poster**

### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR244.05/PP4

**Topic:** I.08. Learning and Memory

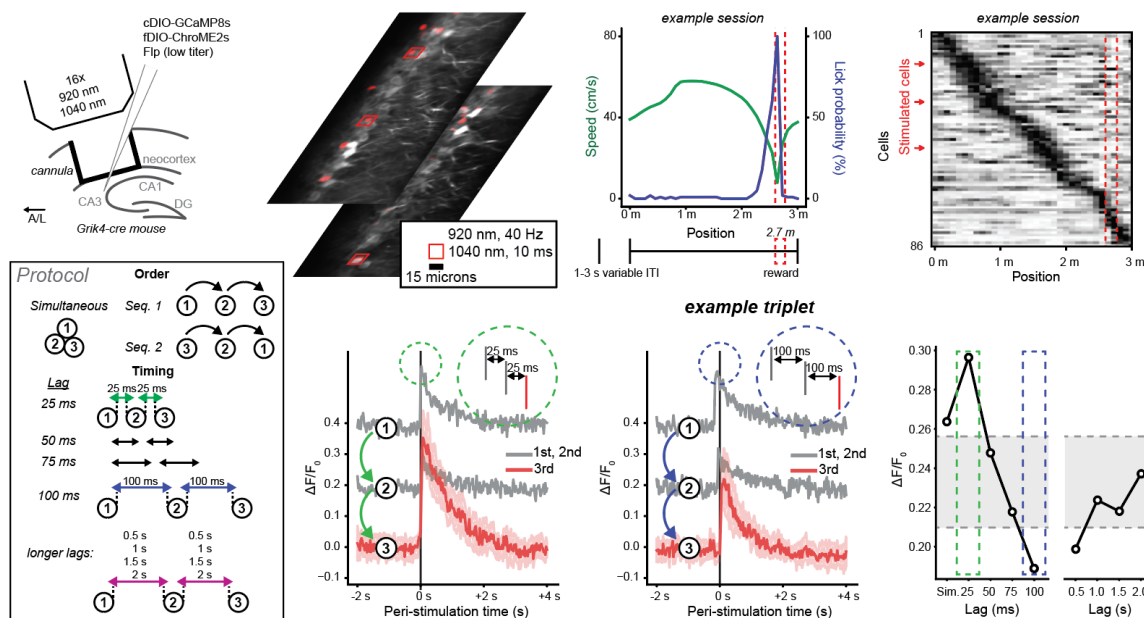
**Title:** Intrinsic dynamics underlying flexible sequence generation in the hippocampus

**Authors:** \*I. VOITOV, A. MUSAD, C. SANTHIRASEGARAN, A. SHAH, A. LOSONCZY; Columbia Univ., New York, NY

**Abstract:** The hippocampus supports sequential neural activity that spans multiple timescales and flexibly reorganizes across contexts. Recurrent circuitry in area CA3 has been implicated in generating sequential activity, but it remains unclear how distinct patterns of activity arise from fixed network dynamics. Here, we used two-photon targeted optogenetic stimulation to activate CA3 neurons in precisely timed sequences with varied orders and temporal lags, allowing us to map the intrinsic interactions shaping network dynamics. We uncovered dense interactions whose strength and sign - facilitatory or inhibitory - changed gradually with stimulation lag at tens-of-milliseconds resolution. We sampled these empirical interactions to build a temporal-kernel RNN and, by analyzing its dynamics, uncovered dense input-dependent phase transitions that enabled it to generate context-specific sequences. To test whether such dynamics support sequences at behavioral timescales, we performed closed-loop experiments by stimulating at millisecond timescales the place field sequences observed during spatial navigation. Intrinsic interactions were stronger for behaviorally relevant sequences and reorganized rapidly upon

remapping to novel environments. Together, our results demonstrate that fast, context-sensitive intrinsic dynamics in CA3 generate reservoirs of flexible spatiotemporal sequences, bridging millisecond-scale network interactions with behavioral timescale computation in the hippocampus.

#### Identifying spatiotemporal interactions in CA3 via sequential optogenetic stimulation



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#### Poster

#### PSTR244: Hippocampal Circuits

**Location:** SDCC Halls B-H

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**Topic:** I.08. Learning and Memory

**Support:** NIMHR01MH124047  
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NINDSU01NS115530  
NINDSR01NS133381  
NINDSR01NS131728  
NIARF1AG080818

**Title:** In vivo dendritic voltage imaging of CA3 pyramidal neurons during spatial learning

**Authors:** \*A. NOGUCHI<sup>1</sup>, G. ZAKKA<sup>2</sup>, C. O'TOOLE<sup>1</sup>, L. REYNOLDS<sup>1</sup>, M. LAND<sup>4</sup>, B. ROZSA<sup>5</sup>, F. ST-PIERRE<sup>6</sup>, A. LOSONCZY<sup>3</sup>, S. TERADA<sup>2</sup>;  
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<sup>4</sup>Baylor Col. of Med., HOUSTON, TX; <sup>5</sup>Inst. Exptl. Med. of HUN-REN, Budapest, Hungary;  
<sup>6</sup>BCM, Houston, TX

**Abstract:** The hippocampal CA3 region is essential for rapid memory encoding and consolidation during sharp-wave ripples (SWRs), owing to its unique circuit architecture characterized by recurrent connections, mossy fibers, and direct entorhinal cortical inputs. Despite decades of work, the in vivo subcellular computational mechanisms of the CA3 network remain poorly understood. To address this question, we implemented ultra-fast, motion-stabilized, three-dimensional voltage imaging along the dendrites and somata of CA3 pyramidal cells during virtual reality-guided navigation. We identified robust place fields across dendritic domains in familiar environments, characterized by spatially tuned burst spikes with large depolarizations tightly coupled to the somatic place field. Distinct patterns of somato-dendritic decoupling emerged during different remapping processes. When the reward location was switched in familiar environments, somatic place fields rapidly adapted, while dendrites initially maintained their original place. In contrast, in mice exposed to novel environments, we observed coordinated formation of the place field starting from dendrites. Furthermore, spatially co-tuned dendrites retained their coordination during subsequent sharp-wave ripple events. Our results provide a deeper mechanistic understanding of how electrical compartmentalization in distinct dendritic domains is organized in CA3 pyramidal neurons during learning.

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## **Poster**

### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR244.07/PP6

**Topic:** I.08. Learning and Memory

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National Institute of Neurological Disorders and Stroke (NINDS) R01NS121106  
National Institute of Neurological Disorders and Stroke (NINDS) Brain Initiative R01NS133381

**Title:** Physiological correlates of transcriptomically defined hippocampal interneurons



**Authors:** \*H. YONG<sup>1</sup>, C. O'TOOLE<sup>1</sup>, M.-E. CONDE PAREDES<sup>1</sup>, S. A. HERRLINGER<sup>1</sup>, J. YOO<sup>4</sup>, T. S. MIHAILA<sup>2</sup>, B. RAO<sup>1</sup>, J. SHI<sup>1</sup>, E. VAROL<sup>5</sup>, A. LOSONCZY<sup>3</sup>;  
<sup>2</sup>MD/PhD Program, <sup>3</sup>Neurosci., <sup>1</sup>Columbia Univ., New York, NY; <sup>4</sup>Zuckerman Inst. at Columbia Univ., New York, NY, ; <sup>5</sup>New York Univ., Brooklyn, NY

**Abstract:** The functional activities of mammalian cortical circuits are shaped by the precise orchestration of gene expression. Understanding this interplay between neural activity and gene regulation is essential for unraveling the mechanisms underlying cortical functions. Recent advances in single-cell sequencing and spatial transcriptomics have provided unprecedented insights into the diverse cell types within the mammalian brain. However, a critical question remains: do these cell types contribute to the functional heterogeneity observed in regions like the hippocampus? Located in the medial temporal lobe, and central to memory and spatial navigation, the hippocampus contains place cells - neurons that encode individual's location in place. While much attention has focused on how excitatory principal cells drive these place-encoding dynamics, inhibitory interneurons are critical for the timing, precision, and overall stability of the hippocampal circuits. Despite their known impact on network activity, our understanding of molecular diversity within this inhibitory population, and its relationship with functional heterogeneity remains incomplete. Here, we addressed this gap by combining in vivo 2-photon functional imaging with spatial transcriptomics (MERFISH) to generate an integrative dataset correlating molecular profiles with the physiological properties of CA1 interneurons. This approach enables the retrieval of genetic profiles from hundreds of chronically imaged cells, revealing previously undetectable subclasses of major interneuron types. Furthermore, functional imaging of these subclasses has uncovered fine-scale differences that could not be identified with traditional methods such as immunohistochemistry. This project aims to comprehensively characterize the functional and genetic diversity of hippocampal interneurons and establish a robust correlation between the two. Ultimately, this dataset will provide a baseline for understanding the role of interneurons in health and can be used to identify disruptions in hippocampal circuitry in disease models.

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## **Poster**

### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

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**Topic:** I.08. Learning and Memory

**Support:** NIH NINDS 1R01NS109362-01  
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NIH NIA T32AG052909  
NYU Langone Health Alzheimer's Disease  
McKnight Endowment Fund

Blas Frangione Foundation  
Mathers Charitable Foundation

**Title:** Characterizing Memory and Place Cell Deficits in an Alzheimer's Disease Mouse Model

**Authors:** \*A. OLERU<sup>1</sup>, J. J. MOORE<sup>3</sup>, M. HOPKINS<sup>4</sup>, M. V. CHAO<sup>2</sup>, J. BASU<sup>5</sup>;  
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**Abstract:** Alzheimer's disease (AD) patients, even in the mild cognitive impairment stage, show pronounced memory impairment that correlates with AD pathology in the entorhinal cortex (EC) - hippocampus circuit. Within the EC-hippocampal network, the lateral EC (LEC) and hippocampal area CA1 are most susceptible. Yet, there is a gap in our knowledge of potential cellular targets and pathway-specific neuromodulatory mechanisms for devising effective and translatable early-stage therapeutic strategies in humans. Our study examines the GABAergic microcircuits within mouse CA1, specifically those driven by vasoactive intestinal peptide (VIP+) and somatostatin (SST+) inhibitory neurons (INs) that gate activity from entorhinal cortex (EC), with the hypothesis that modulating activity in these two circuits can improve EC-CA1 dynamics and related memory-guided behavior. This hypothesis is bolstered by circuit mapping data showing that disinhibition by VIP+ INs and inhibition by downstream SST+ INs gates EC driven dendritic excitation of CA1 pyramidal neurons (PN) dendrites. This circuit in turn may be tuned by cholinergic neuromodulation. We have conducted a comparison of GABAergic circuits in the area EC and CA1 of an AD mouse model (APP-KI) to identify which cell types show pathological resilience and vulnerability across different disease stages. Using *in vivo* two-photon calcium imaging in awake-behaving mice performing a contextual tone and odor-cued spatial memory behavior we found that place cell activity is impaired in AD mice along with a lag in behavioral learning. Our preliminary data suggest that place cell remapping deficits can be rescued by restoring CA1 activity through chronic cholinergic neuromodulation.

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**Poster**

**PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR244.09/PP8

**Topic:** I.08. Learning and Memory

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**Title:** Long-term dynamics of dendrites and dendrite-targeting inhibitory neurons in mouse CA3

**Authors:** \*J. J. MOORE<sup>1,2</sup>, R. BATOOL<sup>1</sup>, J. GROTH<sup>1</sup>, J. BASU<sup>3</sup>;

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**Abstract:** Neurons maintain large dendritic arbors supporting non-linear input integration which can greatly boost their computational power. Recent work suggests that synaptic plasticity induced by dendritic plateau potentials underlies new place field formation in the hippocampus, highlighting the functional relevance of dendrites to memory formation. But the modulation of hippocampal dendritic activity supporting memories over long timescales has not been characterized. Are there dendritic compartment-level differences in the stability and flexibility of spatial representations? How does inhibition targeted to specific compartments affect the way in which different inputs affect somatic output? To address these questions, we imaged calcium activity of dendrites and soma of pyramidal neurons and dendrite-targeting somatostatin expressing (SST) neurons in area CA3 of headfixed mice. We virally expressed GCaMP in either population, allowing simultaneous imaging of soma and dendrites of labeled neurons. Mice performed a random foraging task on a linear treadmill belt with different tactile cues defining position. We introduce a “Möbius belt,” a treadmill belt with different cues on either side, to enable switching environments (A and B) during continuous imaging, capturing rapid context-driven learning and remapping of place soma and dendrites. Mice had to operantly lick to one of two available water ports in either environment for sugar-water rewards. Neurons were longitudinally imaged for one week during familiarization with environment A. Imaging continued for another week with sessions switching between environments A and B. This longitudinal imaging allows us to examine the stability of spatial representations. We observed that apical dendrites had higher levels of stability compared to basal dendrites, with better position decoding across days. These compartment-level differences in tuning stability may arise from the functional differences in the stratified inputs that target different dendritic compartments results in compartment-level differences in tuning. Both soma and dendrites of pyramidal neurons exhibited remapping between the two environments. While some SST neurons showed spatial selectivity that remapped, others modulated their overall activity levels, preferring either the familiar or novel environment. This modulation may support pyramidal neuron remapping by altering the landscape of dendritic inhibition. These experiments offer a unique and detailed view into how the hippocampus incorporates new information as novel environments become familiar, and how multiple memories interact with each other.

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**Poster**

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**Topic:** I.08. Learning and Memory

**Support:** NIH NINDS 1R01NS109362-01  
BRAIN INITIATIVE 1R01NS109994

**Title:** Investigation on the Role of Inhibition in Behavioral Timescale Synaptic Plasticity in Hippocampal CA1

**Authors:** \*S. WANG<sup>1</sup>, J. BASU<sup>2</sup>, R. W. TSIEN<sup>3</sup>;

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**Abstract:** Behavioral Timescale Synaptic Plasticity (BTSP) enables rapid, one-shot formation of hippocampal place fields through dendritic calcium plateau potentials, but the role of inhibition in this process remains poorly understood. Originally, BTSP has been induced in acute slices with pharmacological blockage of inhibition, although *in vivo* inhibition is intact and actively modulated during place cell tuning, for which BTSP is proposed as an underlying mechanism. This poses the question whether BTSP can be induced in the presence of inhibition *ex vivo*, and if so, whether BTSP modulate inhibitory activity. To address these questions, we performed whole-cell current clamping recording on mouse acute hippocampal slices in area CA1. We were able to induce BTSP with inhibition intact but found that the level of potentiation derived from postsynaptic potentials (PSPs, a combination of excitatory and inhibitory inputs) was reduced compared to when GABA receptors were blocked. We hypothesized that inhibition gates the excitatory input-output transformation function to suppress BTSP. To test this, we isolated excitatory postsynaptic currents (EPSCs) using whole-cell voltage clamp recordings to see if EPSCs were differentially modulated with and without inhibition. Surprisingly, we found that EPSCs were equally potentiated with or without intact inhibition. This suggests that BTSP entails a purely excitatory component (E-BTSP), which remains even with inhibition intact. Furthermore, this raises the possibility that inhibitory transmission itself is modulated during BTSP (I-BTSP). We are now exploring the effect of BTSP on coordinated activity of excitatory and inhibitory synapses.

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**Topic:** I.08. Learning and Memory

**Support:** NIH NINDS 1R01NS109362-01  
NIH BRAIN Initiative 1R01NS109994  
NIH NIMH T32

**Title:** Circuit interactions of the medial and lateral entorhinal cortices in hippocampal area CA3

**Authors:** \*K. M. O'NEIL<sup>1</sup>, V. ROBERT<sup>2</sup>, J. BASU<sup>3</sup>;

<sup>1</sup>Neurosci., New York University, Sch. of Med., New York, NY; <sup>2</sup>NYU Neurosci. Inst., New York Univ. Langone Med. Ctr., New York, NY; <sup>3</sup>Dept. of Neurosci. and Physiol., NYU Neurosci. Inst., New York, NY

**Abstract:** Our memories rely on the association of information from different sensory modalities but how this information is conveyed at a single neuron level remains an open question. The entorhinal cortex provides complex sensory information to the hippocampus and is subdivided into the lateral (LEC) and medial entorhinal cortex (MEC). Longstanding dogma assumes that the association of place (MEC) and context (LEC) is key to forming stable and flexible hippocampal representations. To understand how space and context are implemented in the episodic memory system I looked at the functional, circuit interactions of LEC and MEC inputs to CA3. For this, I used dual-color optogenetic stimulation of LEC and MEC inputs and *ex vivo* whole-cell patch-clamp recordings from CA3 pyramidal neurons together with pharmacology to examine the input-output transformation operated by this circuit. I found that every CA3 pyramidal neuron recorded was monosynaptically connected to both MEC and LEC inputs. Recordings of excitatory and inhibitory postsynaptic currents suggest MEC and LEC recruit similar amounts of excitation and inhibition, despite their difference in anatomical proximity and overall coverage. Though stimulation of an individual input (MEC or LEC) does not lead to action potential generation, in a fraction of CA3 pyramidal neurons, simultaneous or near-simultaneous (0.1-10ms) stimulation of both inputs can lead to somatic output. This suggests synchronization of EC inputs with CA3 firing may require MEC and LEC coincident activity, a phenomenon thought to be responsible for efficient transfer of information from one brain region to another. To find the mechanism for 'filtering' and/or integrating the signal from LEC and MEC I looked at the microcircuitry modulating each input at the level of CA3. Our findings indicate that these inputs recruit overlapping interneuron subtypes (CCK, PV, and VIP). However, when we stimulated these inputs at relevant *in vivo* frequencies we found a frequency dependent change in the short-term plasticity dynamics of the LEC to CA3 circuit but not the MEC to CA3 circuit. At the network level frequency has been shown to convey region specific information *in vivo*, in support of this my findings indicate this also holds true at the single neuron level. My study provides both structural and functional evidence that surprisingly, MEC and LEC circuits are similar in terms of the downstream response but likely convey independent information via their dynamics, ie frequency and timing.

**Disclosures:** K.M. O'Neil: None. V. Robert: None. J. Basu: None.

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**Topic:** I.08. Learning and Memory

**Support:** 5TL1TR001447-10  
5T32NS086750-07

**Title:** Stable hippocampal CA1 ensembles are supported by cognitive demand and entorhinal cortex

**Authors:** \*M. HOPKINS<sup>1</sup>, P. RAHAL<sup>1</sup>, J. BASU<sup>2</sup>;

<sup>1</sup>New York Univ., New York, NY; <sup>2</sup>Dept. of Neurosci. and Physiol., NYU Neurosci. Inst., New York, NY

**Abstract:** Place cells, hippocampal pyramidal neurons which show location-specific activity during navigation, form a spatial map of the environment. They are hypothesized to be the neural substrate of episodic memory. However, place cells in low demand unstructured tasks or cue deprived environments, tend to drift in their spatial tuning over days. Through chronic 2-photon calcium imaging of hippocampal area CA1 across weeks, we directly compare stability in a low demand task against stability in a high demand task within the same animal over the course of learning and recall in the same environment. We find that compared to random foraging, an odor-context based navigational task stabilizes place cell representations and increases place cell quality and quantity. To further investigate synaptic input and circuit mechanisms that may support this stability, we interrogated the effect of manipulating excitatory drive from lateral entorhinal cortex (LEC), which provides both indirect and direct multisensory inputs about context, odor, and time to CA1. We chemogenetically suppressed activity of excitatory neurons in LEC during recall of the odor-context based navigation task and found that context discrimination is impaired at both the behavioral and neural level. Our study finds that increasing task demand increases CA1 stability and that this stability is partially supported by lateral entorhinal cortex.

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**Topic:** I.08. Learning and Memory

**Support:** SNF P2EZP3\_181896  
R01 MH104602

**Title:** Distinct role for hippocampal CA1 and CA2 region in social fear extinction

**Authors:** \*P. KASSRAIAN<sup>1</sup>, S. A. SIEGELBAUM<sup>2</sup>;

<sup>1</sup>Columbia Univ., New York, NY; <sup>2</sup>Dept of Neurosci., Columbia Univ. Postdoctoral Dept. of Neurosci., New York, NY

**Abstract:** Prior work has demonstrated that the hippocampal cornu ammonis 2 (CA2) region is critical for social novelty recognition memory (SNRM) but not for canonical hippocampus-dependent spatial and contextual memory. In our recent work, we have demonstrated that CA2 pyramidal neurons (PNs) are also required for a form of social episodic memory: CA2 PNs mediate the learned discrimination between threat-associated (CS+) and safety-associated (CS-) conspecifics (termed social fear discrimination memory; SFDM). CA2 silencing results in generalized social avoidance, reminiscent of generalized social avoidance behaviors. Using in vivo one-photon calcium imaging, we found that SFC increased both the proportion and stability of CA2 PNs that encode CS+ and CS- identities. Of particular interest, CA2 representations provide a generalized or abstract representation of social valence: A linear decoder trained to discriminate between one pair of CS+/CS- mice generalizes successfully to discriminate another pair of CS+/CS- mice. In contrast, how CA2 mediates the extinction of social fear, and if the CA1 and CA2 regions contribute to distinct components to this process, is not known. Here, using the SFC paradigm, we demonstrate CA2's necessity for social fear extinction: During subsequent exposures to CS+ and CS- conspecifics without reinforcement, silencing CA2 PNs prevents both the decrease in CS- preference and the reduction in anxiety-like behaviors observed in control mice. Using one-photon in vivo calcium imaging, we find that social fear extinction coincides with the emergence of CA2 'extinction cells' responsive to CS+ and CS- after extinction. At the population level, extinction is associated with distinct CA2 social representations, distinguishable from CA2 social representations prior to social fear extinction. In contrast, while social identity can be decoded from CA1 PNs - whose activity is dispensable for social fear extinction - CA1 representations remain stable across SFC encoding, recall, and extinction. This functional divergence correlates with differences in mixed selectivity: CA2 shows a greater proportion of social neurons responsive to footshock, whereas CA1 contains more footshock-responsive place cells.

**Disclosures:** P. Kassraian: None. S.A. Siegelbaum: None.

## **Poster**

### **PSTR244: Hippocampal Circuits**

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**Topic:** I.08. Learning and Memory

**Support:** NIH Grant F31-NS127417  
NIH Grant R01-NS139469  
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**Title:** Hippocampal inhibitory cells target burst-firing supramammillary cells: assessing supramammillary cell identity by firing properties

**Authors:** \*L. GLASSBURN<sup>1</sup>, E. MARRON<sup>2</sup>, E. I. KROOK-MAGNUSON<sup>3</sup>;

<sup>1</sup>Univ. of Minnesota Grad. Program In Neurosci., Minneapolis, MN; <sup>2</sup>Pharmacol., <sup>3</sup>Neurosci., Univ. of Minnesota, Minneapolis, MN

**Abstract:** The supramammillary area (SuM) projects directly to the hippocampus, and has been shown to impact hippocampal theta oscillations, spatial and social processing, and memory. The SuM itself is under inhibitory control from the hippocampus, although very little is known about this connectivity. Previous work established that a nNOS-expressing inhibitory population, termed LINC<sub>s</sub>, projects from the hippocampus to the SuM. Using fluorogold retrograde tracing, we found that inhibitory cells from across the dorsoventral axis and across hippocampal subregions project to the SuM. Many are somatostatin positive (Sst<sup>+</sup>), indicating that hippocampal projections to the SuM consist of both a Sst<sup>+</sup> population and nNOS<sup>+</sup> LINC<sub>s</sub>. Viral tracing further revealed that both Sst<sup>+</sup> and NOS<sup>+</sup> hippocampal inhibitory cells project to both medial (SuMM) and lateral (SuML) supramammillary, as well as both anterior and posterior SuM. Ex vivo optogenetic stimulation coupled with whole-cell patch clamp recordings confirmed functional connectivity. As largely distinct populations of SuM neurons are believed to project to the dorsal versus ventral dentate gyrus, we used retrograde labeling to identify SuM neurons projecting to the dorsal (“SuM→dorsalDG”) or the ventral dentate gyrus (“SuM→ventralDG”). We found inhibitory input to both SuM→ventralDG and SuM→dorsalDG cells. Notably, SuM→dorsalDG cells receive input from both dorsal (1/6 cells, 17%) and ventral hippocampus (6/22 cells, 22%), arguing against a simple feedback loop. This work also indicated that only a subset of hippocampal-projecting SuM neurons receive inhibitory hippocampal input (<25%), indicating possible cell-type specific targeting. SuM cells can be classified by their projection patterns (which did not appear to strongly distinguish between cells receiving hippocampal input and those not), and by other factors, including neurochemical expression and firing properties. We found that cells with a distinctive burst-wave firing pattern at threshold were disproportionately innervated by hippocampal inhibitory neurons (6/13 burst-wave vs. 12/127 non-burst wave; 46% vs. 9%,  $p < 0.001$ , chi square). We intend to further investigate these burst-wave cells to understand their neurochemical and projection identity. Towards that goal, we have found that no recorded SuM nNOS<sup>+</sup> cell displayed burst-firing properties (0/7). Collectively, our data indicates that hippocampal inhibitory projections to the SuM are from both nNOS<sup>+</sup> and Sst<sup>+</sup> populations, and disproportionately target SuM burst-wave cells. Ongoing work will further characterize the neurochemical and projection identities of burst-wave cells of the SuM.

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**Poster**

**PSTR244: Hippocampal Circuits**

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**Topic:** I.08. Learning and Memory

**Support:** T32HD007491  
NIH MH125943  
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Brain Research Foundation School of Medicine Seed Grant

**Title:** Kirrel3-expressing GABAergic neurons in the mouse hippocampus regulate memory precision

**Authors:** \*C. M. PETERSON<sup>1</sup>, A. B.-N. TUNON-ORTIZ<sup>2</sup>, D. TRÄNKNER<sup>4</sup>, M. E. WILLIAMS<sup>3</sup>;

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<sup>3</sup>Neurobio., Univ. of Utah, salt lake city, UT; <sup>4</sup>HHMI-Janelia Farm, Salt Lake City, UT

**Abstract:** GABAergic inhibitory neurons constitute only a small fraction of all neurons and yet they are critical for all aspects of brain function. They are profoundly diverse, and our current understanding of GABA neuron function represents a limited portion of this diversity. Here, we investigated the function of a previously unstudied population of hippocampal GABAergic inhibitory neurons that are identified by expression of the synaptic cell adhesion molecule Kirrel3. We found that activating Kirrel3-GABA neurons with DREADDs inhibits CA3 neuronal activity and decreases memory discrimination. This phenotype is unique to Kirrel3-GABA neurons because it is not observed when we activate parvalbumin neurons. Building on this work, we will present new data investigating precisely when Kirrel3-GABA neuron activation impairs memory (encoding vs recall) and how inhibiting Kirrel3-GABA neurons affects learning and memory. This is especially important given that Kirrel3 variants are implicated in neurodevelopmental disorders. Thus, Kirrel3-GABA neurons and their circuits are likely to be altered in Kirrel3-related disorders. Moreover, this work provides new insights into how GABA neurons in area CA3 regulate memory precision and establishes a framework for the study of inhibitory neurons based on connectivity molecules.

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**Poster**

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**Topic:** I.08. Learning and Memory

**Support:** NSFC Grant 32071025

**Title:** A perirhinal cortex to hippocampal CA1 direct feed-forward inhibition circuit mediates recognition memory discrimination

**Authors:** J. ZHANG, \*X. HE, X. ZHANG;  
Beijing Normal Univ., Beijing, China

**Abstract:** The perirhinal cortex (PER) is a critical part of the parahippocampal-hippocampal network which has connection with the entorhinal cortex (EC) and the hippocampus (HPC). It is well known that the PER plays an essential role in object-related processing and recognition memory. Previous electrophysiology research has mentioned that in addition to the classic indirect pathway of PER→EC→HPC, there may exist a direct PER→HPC CA1 circuit. However, the synaptic connection map and function of this PER→CA1 circuit remain completely unknown. By using the optogenetic channel ChR2-assisted circuit mapping (CRACM), we aim to map the functional connections of the PER→HPC direct circuit. In our results, a subpopulation of superficial PER neurons directly project to the board of CA1 *s.r.* and *s.l.m* layer, and preferentially activate a specific subset of inhibitory interneurons (INs) which primarily target CA1 pyramidal neurons. This connection leads to a feed-forward inhibition on CA1 output neurons. Furthermore, we confirmed that those border INs express molecular markers cholecystokinin (CCK) or vasoactive intestinal peptide (VIP), or both, respectively. While confirming the connection of this circuit, we then propose to investigate its function. To determine the activation of this PER direct projection during different memory processing, we use fiber photometry to record the PER projecting axonal Ca<sup>+</sup> activities in CA1. The results indicate that PER axons were strongly activated in processes of object exploration or contextual memory retrieval. With optogenetic suppression, we found that suppressing the axonal activity of this circuit impairs object discrimination and controls the scale of contextual memory generalization, respectively. In conclusion, our findings suggest that in addition to the classic pathway to CA1 across multiple regions, PER also exerts direct feed-forward inhibition to regulate CA1 output activity that controls memory discrimination.

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**Topic:** I.08. Learning and Memory

**Support:** NIH Grant RF1MH130422

**Title:** The Symmetry and Asymmetry of Entorhinal-Hippocampal Dialogue in Memory

**Authors:** U. SALEEM<sup>1</sup>, A.-V. LE<sup>1</sup>, L. MUNOZ<sup>1</sup>, K. ZHAO<sup>1</sup>, T. PANCHUMARTHY<sup>1</sup>, Y. LI<sup>1</sup>, \*W. XU<sup>2,1</sup>;

<sup>1</sup>Dept. of Neurosci., The Univ. of Texas Southwestern Med. Ctr., Dallas, TX; <sup>2</sup>UT Southwestern, Dallas, TX

**Abstract:** Episodic memory retrieval is often conceptualized as a neural "re-instatement" of brain activity patterns from encoding. During encoding, multi-modal sensory information converges through cortices, ultimately funneling via parahippocampal/perirhinal regions into the entorhinal cortex (EC) and hippocampus to form "memory indexes." Cues are thought to engage these indexes during retrieval, reactivating distributed neuronal ensembles via pathways that mirror encoding streams in reverse. The anatomical basis for this proposed encoding/retrieval symmetry remains unclear. We investigated the crucial bidirectional connections between EC and hippocampal CA1 to elucidate this. Employing concurrent anterograde and retrograde viral tracing from precisely targeted CA1 subregions, we unveiled a complex interplay of both symmetric and asymmetric connectivity. Firstly, the anterior portion of the dorsal CA1 (dCA1a) exhibits a classic reciprocal relationship with dorsal medial EC (MEC). MEC Layer 3 (L3) neurons project to dCA1a, while dCA1a robustly projects back to MEC Layer 5 (L5) neurons within the same anatomical domain. This architecture suggests a direct, mirrored pathway for information ingress (EC-to-CA1) and egress (CA1-to-EC), potentially supporting high-fidelity memory reinstatement. Secondly, the proximal dorsal CA1 (dCA1p) also shows regional reciprocity with EC (L3 input, L5 output). Critically, we observed an additional, significant projection from these dCA1p back to EC L3. This CA1-to-EC L3 loop may facilitate rapid feedback. And thirdly, the ventral portion of dorsal CA1 (dCA1v) shows pronounced asymmetric connection to EC: substantial EC territories project to dCA1v but do not receive reciprocal projections from the same CA1 subregion. Conversely, other EC zones receive inputs from dCA1v but lack projections back to their CA1 afferent source. These findings challenge simplistic notions of symmetric encoding/retrieval pathways, revealing a nuanced circuit design. We are now advancing tracing technologies to dissect these principles at single-neuron resolution and functionally determine how symmetric and asymmetric motifs differentially contribute to the multifaceted processes of learning and memory. (The authors US, LA, ML, and KZ made equal contributions to this study.)

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## **Poster**

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**Topic:** I.08. Learning and Memory

**Support:** JST PRESTO Grant JPMJPR21S3  
JST CREST Grant JPMJCR21P3

**Title:** Distinct lateral entorhinal circuits convey olfactory and gustatory cortical inputs to the hippocampus in rodents

**Authors:** \*S. OHARA, T. KAWAMURA, K.-I. TSUTSUI;  
Tohoku Univ. Grad Sch. Life Sci., Sendai, Japan

**Abstract:** Multisensory information converges in the lateral entorhinal cortex (LEC) and is transmitted to the hippocampus via projections originating from its superficial layers. This anatomical arrangement has led to the idea that LEC plays a crucial role in integrating sensory inputs to support episodic memory formation. However, axons from different sensory cortices terminate in distinct LEC layers: the piriform cortex (PC), which processes olfactory information, projects to layer 1, whereas the insular cortex (IC), responsible for gustatory information, targets deeper layers. These laminar differences raise the possibility that olfactory and gustatory inputs are not integrated within shared circuits but instead are processed by distinct modality-specific circuits. To test this hypothesis, we examined the LEC pathways that convey sensory information to the hippocampus by using retrograde transsynaptic with rabies viral vectors (RV) in rats. RV injections into the dentate gyrus (DG) labeled neurons in the PC and layer 2 of the LEC, with minimal labeling in the IC. In contrast, RV injections into both DG and CA1 resulted in additional labeling in the IC and in layer 3 of the LEC. These findings indicate that olfactory information is mainly transmitted from the PC to DG via LEC layer 2 neurons, whereas gustatory information is conveyed from the IC to CA1 via LEC layer 3 neurons. We further investigated the organization of these LEC circuits by focusing on the GABAergic neurons, which likely contribute to sensory gating. Using a modified anterograde transsynaptic tracing approach with adeno-associated virus serotype 1 (AAV1) in mice, we labeled LEC neurons receiving inputs from either the olfactory bulb (OB) or the IC. To determine the cell types of these labeled neurons, we performed immunostaining for glutamate decarboxylase to identify GABAergic neurons. The proportion of GABAergic neurons was lower in the OB-LEC circuit compared to the IC-LEC circuit, suggesting reduced feedforward inhibition in olfactory pathways relative to gustatory pathways. This difference in inhibitory modulation was further supported by ex vivo electrophysiological recordings. Together, these findings reveal that the olfactory and gustatory information are processed in distinct LEC circuits and routed to different hippocampal subregions. This anatomical organization may provide new insight into how different sensory modalities contribute to episodic memory formation.

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**Topic:** I.08. Learning and Memory

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NSF OIA-2121164

**Title:** Mapping the Connectomic Heterogeneity of Subiculum Cell Types in the Mouse Brain

**Authors:** \*A. W. SAUSTAD<sup>1,2</sup>, M. S. BIENKOWSKI<sup>1,2</sup>;

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**Abstract:** The subiculum (SUB) is the main output structure of the hippocampus, influencing diverse behaviors through its widespread cortical and subcortical connections. Although the SUB is classically divided into dorsal and ventral subregions, recent studies reveal a more complex anatomical organization. Our previous work, the Hippocampus Gene Expression Atlas (HGEA), identified four genetically distinct cellular layers across five columnar domains in the mouse SUB. Injections of anterograde and retrograde tracers into the SUB and connected brain regions showed similar gene expression and connectivity patterns. Multiscale network analysis revealed that SUB regions are part of three brain-wide systems involved in spatial navigation, social behavior, and neuroendocrine regulation. Recently, a mouse hippocampal single-neuron projectome study generated hundreds of full 3D reconstructions of SUB neurons (Qiu et al., 2024), providing high-resolution insights into their brain-wide projections and axon collateralization at the single-cell level. However, because this dataset was aligned to the Allen CCFv3, it was unclear how these neurons mapped onto the HGEA framework. Using the Mouse Projectome Atlas Digital Brain tool, we conducted ‘virtual tract-tracing’ to assess whether connectivity patterns from 3D reconstructions aligned with those described in the HGEA and whether these neurons could be classified into HGEA-defined SUB cell types. In total, we classified 689 SUB projection neuron cell types into 12 HGEA groups based on their differential laminar and columnar distributions. The localization of their somas and dendrites recapitulated the SUB HGEA-defined 3D boundaries. By analyzing the cell type-specific features in each group, we characterized the heterogeneity of connectivity within each cell type group, identified the common connectivity motifs and collateralization patterns, and defined distinct projection themes for each SUB neuron type. These themes revealed complex axon branching targeting the medial mammillary nucleus (MM), ventral retrosplenial cortex (RSPv), nucleus accumbens, amygdala, and septo-hippocampal system. Notably, over 80% of dorsal SUB neurons in the Mouse Projectome Atlas collateralized to both MM and RSPv, exceeding prior dual-retrograde tracing estimates. This analysis integrates data from the HGEA and the Mouse Projectome Atlas to provide insights into the anatomical organization of SUB cell types and their contributions to brain-wide neural networks that regulate different behaviors.

**Disclosures:** A.W. Saustad: None. M.S. Bienkowski: None.

**Poster**

**PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR244.20/PP19

**Topic:** I.08. Learning and Memory

**Title:** Bridging the mind and body in the hippocampus connectome

**Authors:** \*C. WEINBERGER<sup>1</sup>, M. S. BIENKOWSKI<sup>3</sup>, S. E. KANOSKI<sup>4</sup>, L. F. BARRETT<sup>5</sup>, J. HUTCHINSON<sup>2</sup>;

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**Abstract:** We examined the pattern of hippocampal structural connectivity to other regions of the rat brain to assess how connectivity with cortical regions (typically the focus of studies in learning and memory) resemble or differ from subcortical regions (typically the focus of studies in feeding behavior and energy regulation). We used a novel approach that combines Representational Similarity Analysis (RSA; Kriegeskorte et al., 2008) with Uniform Manifold Approximation and Projection (UMAP; Healy et al., 2024) to analyze efferent hippocampal structural connectivity data within the rat brain connectome (Swanson et al., 2024). Connectivity profiles across each major hippocampal subregion (dentate gyrus, CA3, CA2, ventral and dorsal CA1, and ventral and dorsal subiculum) were analyzed for every parcel across the whole brain. Clustering based on RSA connection profiles yielded two major clusters that include both cortical and subcortical connections. Quantitative analysis of efferent connectivity patterns showed that on average, 32.4% of regions within each cluster were cortical, indicating that hippocampal connectivity is organized by integrative connection patterns rather than by gross anatomical divisions. These findings suggest a model of the hippocampus as a hub that integrates and distributes information across cortical and subcortical regions and suggest the possibility that signals from subcortical regions involved in feeding and energy homeostasis may be positioned to play a crucial role in hippocampal computations underlying learning and memory. Healy, J., & McInnes, L. (2024). Uniform manifold approximation and projection. *Nature Reviews Methods Primers*, 4(1), 1-15. <https://doi.org/10.1038/s43586-024-00363-x> Kriegeskorte, N., Mur, M., & Bandettini, P. A. (2008). Representational similarity analysis—Connecting the branches of systems neuroscience. *Frontiers in Systems Neuroscience*, 2. <https://doi.org/10.3389/neuro.06.004.2008> Swanson, L. W., Hahn, J. D., & Sporns, O. (2024). Neural network architecture of a mammalian brain. *Proceedings of the National Academy of Sciences of the United States of America*, 121(39), e2413422121. <https://doi.org/10.1073/pnas.2413422121>

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## **Poster**

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**Topic:** I.08. Learning and Memory

**Support:** ANR-21-CE16-0021-03  
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Fondation pour la Recherche Médicale EQU202003010457

**Title:** Hippocampal circuit underlying the encoding of novel appetitive food

**Authors:** \*R. A. PISKOROWSKI<sup>1</sup>, H. E. M. ABDELRAHMAN<sup>2</sup>;

<sup>1</sup>Sorbonne University, Inst. Biol. Paris Seine, Neurosci. Paris Seine, Paris, France; <sup>2</sup>Ctr. de Neuroscience, Institut Biologie Paris Seine, Sorbonne Univ., Paris, France

**Abstract:** For optimal learning and survival, novel experiences must be prioritized over familiar ones. The hippocampus plays a key role in memory formation, and area CA2 has been proposed as a novelty detector, integrating sensory inputs and familiarity signals from CA3. However, CA2 pyramidal neurons (PNs) are highly resistant to NMDA-mediated long-term potentiation (LTP), raising questions about how novelty-induced learning occurs at the synaptic level. We hypothesize that dopamine (DA) release during novelty exposure acutely modifies CA2 physiology, enhancing hippocampal output. To test this, we exposed mice to a novel appetitive food, sweetened condensed milk (SCM), and examined synaptic transmission in CA2. We found that brief SCM exposure enabled robust LTP at CA3-CA2 synapses, requiring NMDA receptor activation. Pharmacological experiments revealed that activating dopamine receptors enhanced synaptic transmission, and facilitated activity-induced LTP. Additionally, repeated exposure to SCM abolished experience-induced changes in plasticity, confirming that novelty exposure is inducing changes in CA2 PNs. To assess the impact of novelty-induced changes in CA2 on hippocampal circuitry, we used extracellular recordings in CA1 with either CA2 attached or lesioned. When CA2 was attached, excitatory drive at CA3-CA1 synapses was significantly increased following dopamine receptor activation, suggesting area CA2 modulates hippocampal output following reward. Finally, we found that activating D1/D5 is necessary for SCM induced LTP. This project will clarify CA2's role in novelty-induced learning and hippocampal function, as well as advancing our understanding of DA-mediated plasticity.

**Disclosures:** R.A. Piskorowski: None. H.E.M. Abdelrahman: None.

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### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR244.22/QQ1

**Topic:** I.08. Learning and Memory

**Support:** NIH Grant 1R01HD100607

**Title:** Time-limited neonatal GABAB receptor antagonist treatment results in prolonged normalization of hippocampal synaptic plasticity in Ts65Dn mice, a genetic model of Down syndrome

**Authors:** S. M. NGUYEN<sup>1</sup>, C. FERNANDEZ<sup>2</sup>, C. SPENCER<sup>2</sup>, \*A. M. KLESCHEVNIKOV<sup>3</sup>;

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**Abstract:** Down syndrome (DS) is associated with developmental delays and disrupted neural circuit formation, notably involving enhanced GABAergic signaling. The Ts65Dn mouse is the most widely studied genetic model of DS. We hypothesized that changes in synaptic connectivity and the efficiency of GABAergic neurotransmission in mouse models of DS might result from enhanced GABAB/Girk2 signaling during the formation of nascent neural circuits. In previous studies, we demonstrated that neonatal (P3-P15) treatment of Ts65Dn mice with the GABAB antagonist CGP35348 normalizes the inhibitory/excitatory balance and synaptic plasticity when measured at P21-P28, a stage when neural circuit formation is nearly complete. In this study, we examine whether the effects of neonatal GABAB receptor antagonist treatment persist into adulthood. **Methods:** The GABAB receptor antagonist CGP35348 (10 µg/kg) or vehicle was administered via intraperitoneal (i.p.) injections daily to neonatal Ts65Dn and normosomic (2N) littermate control mice from postnatal day 3 (P3) to P15. To evaluate the enduring effects of the neonatal treatment, animals were examined at 2-5 months of age. Long-term potentiation (LTP) was induced and recorded in the CA1 region of acute hippocampal slices. **Results:** Four groups of animals were examined: 2N Vehicle (2N Veh), 2N CGP35348 (2N CGP), Ts65Dn Vehicle (Ts65Dn Veh), and Ts65Dn CGP35348 (Ts65Dn CGP). Consistent with previous observations, vehicle-treated Ts65Dn mice exhibited a reduced level of LTP compared to vehicle-treated 2N littermate controls ( $118.6 \pm 6.3\%$  vs.  $133.6 \pm 5.1\%$ ,  $p = 0.037$ ). Treatment with CGP35348 significantly improved synaptic plasticity in Ts65Dn mice to control levels ( $133.8\%$ ,  $p = 0.49$  vs. 2N Veh group). The treatment had no significant effect on LTP in 2N mice (2N Veh:  $133.6 \pm 5.1\%$ ; 2N CGP:  $136.9 \pm 8.5\%$ ,  $p = 0.36$ ). **Conclusion:** These findings demonstrate that time-limited neonatal treatment of Ts65Dn mice during the critical period of nascent neural circuit formation restores synaptic plasticity, with the effects persisting into adulthood. This intervention, specifically targeting GABAB signaling, produces a prolonged rescue of hippocampal synaptic plasticity. Our results support the potential of early, targeted pharmacological modulation of GABAergic signaling as a strategy to mitigate persistent cognitive deficits associated with Down syndrome. Such approaches should be further explored as promising therapeutic avenues to improve cognitive function in individuals with Down syndrome.

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## **Poster**

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**Topic:** I.08. Learning and Memory

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**Title:** Three Activity States of Hippocampal Principal Neurons: the Silent, Primed, and Engaged

**Authors:** L. WANG<sup>1</sup>, Y. ZHOU<sup>3</sup>, M. LYON<sup>2</sup>, \*X. CHEN<sup>1</sup>;

<sup>2</sup>Mathematics and Statistics, <sup>1</sup>Univ. of New Hampshire, Durham, NH; <sup>3</sup>Boston Univ., Boston, MA

**Abstract:** It is widely thought that the “activation” of engram cells in memory-related regions during learning and their “re-activation” during recall mediate memory acquisition and retrieval, respectively. Thus, engram neurons are perceived to have two activity states: the silent and activated. However, based on *in vivo* calcium and FosGFP imaging on freely behaving mice, we found that hippocampal principal neurons exhibit at least three distinct activity states relating to associative learning. They are termed the silent, primed, and engaged states, as distinguished by their activity levels, sensitivity to sensory stimuli, Fos expression level, synchronization levels, calcium dynamics, and importantly learning or memory-engaging status. During the period when a small fraction of “primed” neurons fulfills mnemonic duties by transitioning back and forth between the primed and engaged states, most hippocampal neurons exhibit very weak activity and stay in the silent state. We show evidence that the NMDA receptors is a key factor that controls the “silent-primed” neural activity hierarchy in the neural network. We propose that an associative memory is acquired, not simply due to neuronal “activation”, but because the primed neurons are induced to transition from the primed to the engaged state. Likewise, a memory is retrieved, not simply due to neuronal “re-activation”, but because the same subset of memory-holding primed neurons is induced to transition to the engaged state. It is crucial for the brain to maintain the homeostasis of activity states, i.e., the appropriate percentage of primed and silent neurons and their dwelling time in individual states. This is important not only for memory formation and cognitive function, but also for sustaining mental health, because imbalances of activity-state transitions may lead to various mental diseases including dementia, autism, schizophrenia, and epilepsy.

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**PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR244.24/QQ3

**Topic:** I.08. Learning and Memory

**Support:** ZIAMH002784

**Title:** Effects of acute and chronic subregional silencing of adult-born hippocampal neurons on hippocampal network activity

**Authors:** \*N. FREEDGOOD<sup>1,2</sup>, H. A. CAMERON<sup>1</sup>;

<sup>1</sup>Natl. Inst. of Mental Hlth., Bethesda, MD; <sup>2</sup>Neurosci., Brown Univ., Providence, RI

**Abstract:** The dentate gyrus (DG) of the hippocampus is one of few regions in the mammalian brain that continues to generate new neurons throughout adulthood. These adult-born neurons (ABNs) exhibit enhanced plasticity and hyperexcitability, and they have been shown to alter physiology and behavior despite constituting only 3% of the total DG granule cell (GC) population. While extensive research has investigated the functional role of ABNs at the cellular or behavioral levels, few studies have bridged the gap by exploring their effects at the network level. In this study, we optimized two methods for specifically targeting and silencing ABNs in the dorsal or ventral hippocampus in both male and female Long Evans rats. For the acute silencing, we injected a Moloney murine leukemia retrovirus into the DG to express GFP and the chemogenetic receptor hM4Di in the ABNs. When the transfected ABNs reached 4-weeks-old, we administered either clozapine-N-oxide (CNO) to silence the cells, or saline as a control before examining network activity. For the chronic ablation, low-dose Iodine-125 brachytherapy seeds were implanted above the skull in targeted locations. Hippocampal network activity was assessed by counting cells expressing the immediate early gene c-Fos in specific hippocampal neuronal populations after rats explored a novel environment to stimulate hippocampal activity. Acutely silencing 4-week-old ABNs with CNO significantly reduced the density of c-Fos positive cells in the CA3, the primary target of GCs, within only the targeted subregion (dorsal or ventral), with the opposite region unaffected. Silencing ABNs also decreased activity throughout the GC population, again, only within the target subregion. Mossy cells, which receive inputs from ABNs and project to mature GCs, also showed diminished activity, suggesting that they might drive the observed decrease in mature GC activity after ABN silencing. In contrast, our preliminary findings did not show any changes in c-Fos expression in chronically irradiated animals. These results demonstrate that acutely altering the activity of even a small population of ABNs can significantly influence hippocampal network dynamics within the dorsal or ventral subregions. However, chronic loss of ABNs in either subregion may not alter hippocampal activity during a novel experience.

**Disclosures:** N. Freedgood: None. H.A. Cameron: None.

## **Poster**

### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

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**Topic:** I.08. Learning and Memory

**Support:** NIMH RO1MH119421  
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**Title:** Systems consolidation involves reorganization of hippocampal engram circuitry

**Authors:** \*S. Y. KO, Y. RONG, A. I. RAMSARAN, X. CHEN, A. J. RASHID, A. MOCLE, J. DHALIWAL, A. AWASTHI, A. GUSKJOLEN, S. A. JOSSELYN, P. W. FRANKLAND;  
The Hosp. for Sick Children, Toronto, ON, Canada

**Abstract:** Episodic memories—high-fidelity representations of past events that initially depend on the hippocampus—do not retain their precision indefinitely. A key advantage of this time-dependent decline in precision is the emergence of event-linked, gist-like memories that can guide behavior in novel but related situations (i.e., generalization). Prevailing models of systems consolidation propose that this loss of memory precision is accompanied by circuit-level reorganization; however, how underlying engram networks are modified remains poorly understood. Here, we show that time-dependent rewiring of hippocampal engram circuitry actively regulates the shift in memory precision associated with systems consolidation. Using engram labeling and manipulation tools in mice, we demonstrate that the passage of time does not erase hippocampal engrams; rather, it remodels DG-to-CA3-to-CA1 engram connectivity, enabling engram neurons to become promiscuously active and support behavior in contexts that no longer match the original training environment. This reorganization requires adult hippocampal neurogenesis: suppressing neurogenesis prevents engram remodeling and preserves precise, context-specific memories, whereas enhancing neurogenesis accelerates reorganization and promotes the emergence of gist-like memories within the hippocampus. These findings suggest that models of systems consolidation require updating to include intra-hippocampal circuit reorganization as a mechanism underlying qualitative shifts in memory precision.

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## **Poster**

### **PSTR244: Hippocampal Circuits**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR244.26/QQ5

**Topic:** I.08. Learning and Memory

**Support:** NIH R00NS116129  
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**Title:** Cholinergic dynamics in the septo-hippocampal system provide phasic multiplexed signals for spatial novelty and correlate with behavioral states

**Authors:** \*F. FAROKHI MOGHADAM<sup>1</sup>, B. GUTIERREZ GUZMAN<sup>1</sup>, X. ZHENG<sup>2</sup>, H. DANNENBERG<sup>1,2</sup>;

<sup>1</sup>Bioengineering, <sup>2</sup>Interdisciplinary Program in Neurosci., George Mason Univ., Fairfax, VA

**Abstract:** In the hippocampal formation, cholinergic input from the medial septum/diagonal band of Broca (MSDB) has been shown to correlate with an animal's movement speed at sub-

second timescales and plays a key role in spatial memory formation. However, it remains unclear whether, and to what extent, sub-second cholinergic activity aligns with brief behavioral and cognitive states involved in encoding novel spatial information. In this study, we used fiber photometry to record the population activity of septo-hippocampal cholinergic neurons at sub-second resolution during a hippocampus-dependent object location memory task in ChAT-Cre mice. Mice were video-tracked, and their posture and exploratory behaviors were analyzed using deep learning methods. To quantify the relationship between cholinergic activity and different behavioral and cognitive states, we applied a linear mixed-effects model (LMM). These variables included movement speed, behavioral states such as locomotion, grooming, and rearing, as well as cognitive states associated with recognizing a familiar object in a novel location. Our results reveal that cholinergic dynamics encode a multiplexed combination of fast and slow signals: (i) fast signals tracking the logarithm of movement speed at sub-second timescales, (ii) phasic responses to spatial novelty during brief episodes of novel object exploration, and (iii) slower signals reflecting environmental novelty on a timescale of several seconds. Additionally, we show fast (sub-second to seconds) cholinergic transients correlate with the initiation and termination of different behaviors, suggesting a role in facilitating transitions in behavioral and cognitive state. These findings provide new insight into how cholinergic modulation contributes to movement speed and the encoding of novel spatial information.

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## **Poster**

### **PSTR244: Hippocampal Circuits**

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**Program #/Poster #:** PSTR244.27/QQ6

**Topic:** I.08. Learning and Memory

**Support:** IBS-R002 A1

**Title:** Dynamic Reorganization of Hippocampal Value Representations During Probabilistic Reward Learning

**Authors:** \*J. SHIN<sup>1</sup>, Y. JEONG<sup>2</sup>, M. JUNG<sup>3</sup>;

<sup>1</sup>KAIST/IBS, Daejeon, Korea, Republic of; <sup>2</sup>Max-planck-Instituts, Planegg, Germany; <sup>3</sup>Korea Advanced Inst. in Sci. and Technol., Daejeon, Korea, Republic of

**Abstract:** Distinguishing between locations of higher and lower value is a fundamental component of adaptive behavior. [OR: Value representation is central to adaptive behavior, enabling organisms to prioritize actions based on expected outcomes.] Although the hippocampus is traditionally known for its role in episodic memory, growing evidence suggests that it also contributes to the encoding and processing of value-related information. However, how hippocampal representations evolve over the course of value learning remains poorly

understood. In this study, we used calcium imaging to monitor hippocampal neural activity over three days of training in a task where animals navigated maze arms associated with different reward probabilities. In the early phase of learning, forward replay of outbound trajectories was biased toward the high-value arm. As learning progressed, this bias diminished, but replay trajectories became increasingly distinct. In addition, value-modulated place cell activity during reward zone approach, as well as value-dependent synchronized calcium activity during rest, emerged only by the third day of training. Notably, these population-level activity patterns were consistent with the increasing specificity of replay content observed across learning. These findings demonstrate that hippocampal representations of value undergo dynamic reorganization depending on the stage of learning. Furthermore, this study establishes a reliable method for detecting replay events from calcium imaging data.

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## **Poster**

### **PSTR244: Hippocampal Circuits**

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**Topic:** I.08. Learning and Memory

**Support:** McDonnell Small Grant GF0013146  
NIH Grant R01DA058613  
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**Title:** Dorsal Hippocampal Dynamics and Circuit Interactions in Opioid Seeking

**Authors:** \*K. IBRAHIM, J. MORON-CONCEPCION;  
Washington Univ. in St. Louis, St. Louis, MO

**Abstract:** The dorsal hippocampus (dHPC) plays a critical role in opioid addiction through its connections with reward and memory systems. Recent work from our lab (Ibrahim et al., 2024) established that optogenetic activation of the dHPC→nucleus accumbens (NAc) projection is sufficient to drive reinforcement behavior, highlighting its role in shaping reward-related behaviors. In addition, the medial septum (MS) modulates hippocampal network dynamics that are fundamental to learning and memory processes. While these anatomical connections are well-documented, significant gaps remain in our understanding of how these distinct pathways - the dHPC→NAc outputs and MS→dHPC inputs - differentially contribute to opioid addiction. To systematically investigate these, we first combined wireless fiber photometry with mice intravenous fentanyl self-administration and observed real-time increases in dHPC→NAc activity during drug-seeking lever presses and fentanyl infusions, suggesting that this pathway is involved in encoding goal-directed opioid seeking. Building on these findings, we examined whether MS→dHPC inputs play a similar reinforcing role through optogenetic stimulation

during self-administration paradigms. Although MS stimulation reliably evoked hippocampal activation, stimulation of MS→dHPC inputs failed to induce reinforcing behavior. This striking dissociation indicated that unlike the dHPC→NAc outputs, MS inputs to dHPC do not directly drive reinforcement, prompting us to investigate alternative roles for this pathway in addiction processes. Thus, in our third experiment, we used in vivo electrophysiology to characterize how opioids alter dHPC network states. We discovered that both systemic morphine administration and exposure to morphine-paired contexts robustly enhanced theta (4-12 Hz) and gamma (30-80 Hz) oscillations - rhythms known to coordinate memory processes. Given the MS's established role in modulating these rhythms, these findings suggest MS→dHPC inputs may instead regulate addiction by shaping the hippocampal network states that underlie drug-context associations. These findings reveal a potential circuit dissociation: dHPC→NAc directly mediates drug seeking while MS→dHPC shapes addiction through network dynamics rather than reinforcement. Our study provides new insight into how hippocampal subcircuits coordinate different aspects of opioid addiction.

**Disclosures:** K. Ibrahim: None. J. Moron-Concepcion: None.

## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.01/QQ8

**Topic:** I.08. Learning and Memory

**Title:** Long-term running supports pattern separation despite transient changes in hippocampal neurogenesis

**Authors:** \*L. ORIHUELA<sup>1</sup>, C. VIVAR<sup>2</sup>;

<sup>2</sup>Department Physiology, Biophysics and Neurosci., <sup>1</sup>CINVESTAV, Mexico City, Mexico

## **Abstract: Introduction**

The dentate gyrus (DG) plays a key role in pattern separation, a process essential for distinguishing similar experiences in episodic memory. Adult hippocampal neurogenesis has been linked to the processing of highly overlapping patterns, possibly by reducing DG activity. Physical exercise, such as voluntary running, improve pattern separation and enhances neurogenesis, but in rodents, neurogenic effect appears transient as proliferation returns to baseline after about a month. However, this view overlooks potential effects on later neurogenic stages like differentiation and survival. This study investigates whether long-term exercise induces neurogenic changes beyond proliferation and how these changes relate to pattern separation. **Methods**

Young male C57BL/6 mice were assigned to short-term (1 month) or long-term (2 months) voluntary wheel running groups. Newborn granule cells (GCs) in the dentate gyrus were labeled with BrdU or a retroviral vector (CAG-GFP) at 3 or 30 days of running—corresponding to the peak and normalization of exercise-induced proliferation. Thirty days later, we assessed the

differentiation, survival, and dendritic morphology of new GCs. Pattern separation was evaluated using a Novel Object Recognition (NOR) test with two levels of difficulty, and neuronal activity was assessed via c-Fos immunohistochemistry. To examine DG excitability, we also analysed the intrinsic electrophysiological properties of mature GCs. **Results**

Running transiently increased hippocampal neurogenesis but consistently promoted a neuronal phenotype regardless of exercise duration. In the NOR test, no differences were observed under low-difficulty conditions. However, under high-difficulty conditions, exercised mice showed improved recognition performance after a 3-hour delay. Exercise reduced c-Fos activation in the inner granule cell layer—where most young GCs reside—without affecting the outer layer, which contains older GCs. Moreover, exercise enhanced the dendritic complexity of new neurons. Electrophysiological recordings revealed no significant changes in the intrinsic properties of mature GCs. **Discussion**

These findings demonstrate that voluntary running supports pattern separation independently of the transient nature of exercise-induced neurogenesis. This sustained improvement may result from enhanced integration and refinement of young granule cell activity within hippocampal circuits.

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## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.02/QQ9

**Topic:** I.08. Learning and Memory

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**Title:** Dentate gyrus engram cells with high reactivation potential

**Authors:** \*S. L. PARYLAK<sup>1</sup>, T. SARRAF SABEDOT<sup>1</sup>, I. S. GALLINA<sup>1</sup>, A. H. MCDONALD<sup>1</sup>, A. L. TUCKER<sup>1</sup>, Q. WANG<sup>1</sup>, S. A. KERK<sup>1</sup>, C. METALLO<sup>2</sup>, F. H. GAGE<sup>1</sup>;  
<sup>1</sup>Lab. of Genet., <sup>2</sup>Salk Inst., La Jolla, CA

**Abstract:** The recruitment and reactivation of engram cells is a critical component of memory formation and recall. In the mouse hippocampus, dentate granule neurons are sparsely active yet

support discrimination between memories of similar events. When dentate granule neurons are recruited into an engram network, they show an unusually strong transcriptional response. In this study, the function of dentate gyrus engram neurons in adult mice of both sexes was studied in response to the encoding of a novel environment. Despite low initial probabilities of activation (1-2%), dentate gyrus engram neurons reactivated at high rates (~40%) in response to reexposure to the same environment. Engram neurons were hyperexcitable in the days following encoding as measured by patch clamp recordings and gradually achieved high, persistent expression of enkephalin-encoding gene *Penk* and sortilin-related receptor gene *Sorcs3* compared to neighboring inactive cells. *Penk* and *Sorcs3* upregulation 24hr after novel environment exposure was replicated using both single-nuclei RNA-Seq and fluorescent in situ hybridization. Subsequent mass spectrometry analyses of the hippocampus revealed elevated levels of sphinganine, an intermediate in de novo sphingolipid biosynthesis, following novel environment exposure. This acute sphinganine increase was concurrent with the early transcriptional response, indicating a potential metabolite signaling mechanism underlying engram formation. These results suggest that recruitment into the engram triggers lasting changes in dentate granule neurons, enabling future reactivation.

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## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.03/QQ10

**Topic:** I.08. Learning and Memory

**Support:** Institute for Basic Science IBS-R001-D3

**Title:** Growth hormone is required for hippocampal engram cell maturation

**Authors:** \*C.-H. KIM<sup>1</sup>, H. PARK<sup>1</sup>, C. KWAK<sup>3</sup>, D. HAN<sup>1</sup>, I. HONG<sup>1</sup>, Y. KIM<sup>4</sup>, Y.-S. LEE<sup>5</sup>, N.-K. YU<sup>4</sup>, B.-K. KAANG<sup>2</sup>;

<sup>2</sup>Sch. of Biol. Sci., <sup>1</sup>Inst. for Basic Sci., Daejeon, Korea, Republic of; <sup>3</sup>Lab. of Neurobio., Seoul, Korea, Republic of; <sup>5</sup>Dept. of Physiol., <sup>4</sup>Seoul Natl. Univ., Seoul, Korea, Republic of

**Abstract:** Memory is stored in specialized cells known as engram cells, but the molecular mechanisms underlying this process remain unclear. We discovered that the initial translation leading to growth hormone (GH) synthesis in active cells is required for engram cell maturation in the dentate gyrus. Time-course experiments with a translation inhibitor suggested that the key molecule is immediately translated during learning. We identified GH as the crucial factor, specifically translated within the first few minutes of consolidation in highly active cells. Blocking GH activity with a dominant-negative (G118R) mutation blocked engram maturation,



whereas facilitating activity-dependent GH uptake alleviated engram maturation deficits caused by translation inhibition. Together, our findings propose GH as a key mediator of hippocampal engram cell maturation.

**Disclosures:** C. Kim: None. H. Park: None. C. Kwak: None. D. Han: None. I. Hong: None. Y. Kim: None. Y. Lee: None. N. Yu: None. B. Kaang: None.

## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.04/QQ11

**Topic:** I.08. Learning and Memory

**Support:** Esther A. & Joseph Klingenstein Fund  
Simons Foundation  
NIH NINDS (NS126725)

**Title:** Epileptiform corruption of dentate spikes in Alzheimer's disease

**Authors:** \*J. M. GROCOTT<sup>1,2</sup>, K. N. ESFAHANY<sup>1,2</sup>, A. L. SCHOTT<sup>1,2</sup>, J. S. FARRELL<sup>1,2</sup>; <sup>1</sup>Neurobio., Boston Children's Hosp., Boston, MA; <sup>2</sup>Neurobio., F.M. Kirby Neurobio. Ctr. and Rosamund Stone Zander Translational Neurosci. Center, Boston Children's Hospital; Harvard Med. Sch., Boston, MA

**Abstract:** Many Alzheimer's disease (AD) patients experience subclinical epileptiform discharges and seizure activity, which is thought to play a significant role in declining cognitive function and memory. Interictal epileptiform discharges (IEDs) are also observed in mouse models of AD, providing a valuable tool for understanding mechanisms of this hyperexcitable state. We previously found that dentate spikes (DS), which are brief (<50msec) large amplitude (>1mV) events in the hilus of the dentate gyrus (DG) of the hippocampus occurring during low arousal behavioral states, are the most synchronous event in the brain and play a key role in spatial navigation and memory. In mouse models of epilepsy, however, the synchronous population activity during DSs may come at the cost of generating IEDs in pathological networks, as we have observed that approximately one third of all IEDs are immediately preceded by DSs. Because of this coupling, we hypothesized DSs may also be prone to pathological conversion to IEDs in AD. We used high-density silicon probes to measure local field potential (LFP) fluctuations in the hippocampus of 5xFAD mice, a transgenic mouse model containing five familial AD mutations, and compared their activity to age-matched littermate controls. We developed a Graphical User Interface for dentate spike analysis and used independent component analysis to separate IEDs from the large LFP fluctuations during DSs. In preliminary experiments, we observed an increase in the rate of DS type 2 (DS2) as well as precise coupling of DS2 to IEDs, with more IEDs preceded by DS2 than chronically epileptic mice (intrahippocampal kainate). Because DS2s are generated by the medial entorhinal cortex

(MEC) inputs, these data provide insight into precisely where and when IEDs are generated. With limited treatments available for patients with AD, neuromodulation strategies aimed at dampening MEC - DG circuitry could suppress IEDs and improve cognitive function in the approximately 40% of AD patients with epileptiform activity.

**Disclosures:** J.M. Grocott: None. K.N. Esfahany: None. A.L. Schott: None. J.S. Farrell: None.

## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.05/QQ12

**Topic:** I.08. Learning and Memory

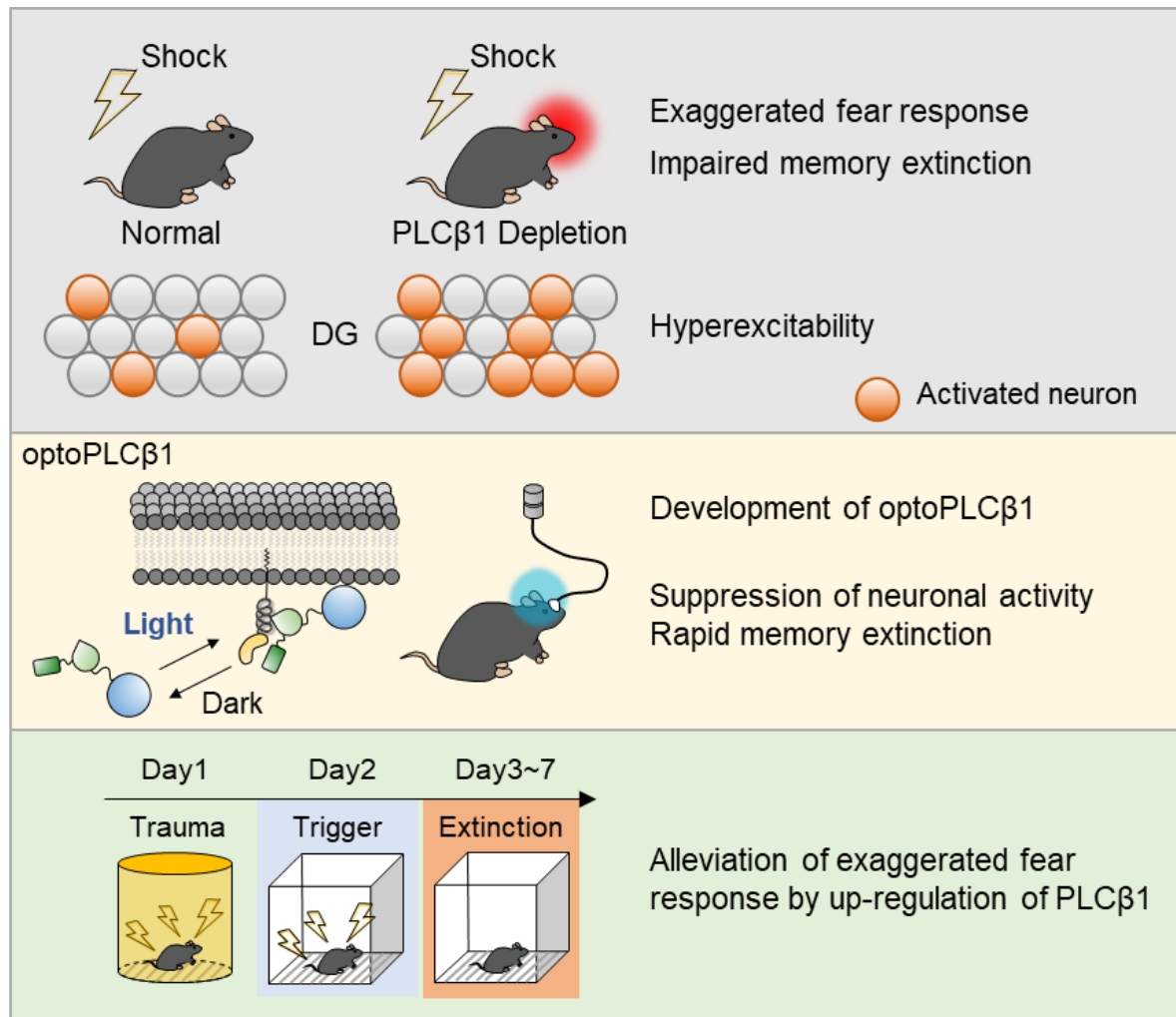
**Support:** KAIST-funded Global Singularity Research Program  
National Research Foundation of Korea

**Title:** Phospholipase beta 1 in the dentate gyrus regulates fear memory formation

**Authors:** \*J. LEE<sup>1,2</sup>;

<sup>1</sup>Brigham and Women's Hospital/Harvard Med. Sch., Boston, MA; <sup>2</sup>Korea Advanced Inst. of Sci. & Technol. (KAIST), Daejeon, Daejeon, Korea, Republic of

**Abstract:** Memory formation is governed by a dynamic molecular signaling network that integrates both facilitatory and inhibitory inputs. Among these, Phospholipase C beta 1 (PLC $\beta$ 1), a key effector downstream of GPCR signaling and highly expressed in the hippocampus, acts as a crucial molecular gatekeeper in contextual fear memory processing. While previous studies linked global PLC $\beta$ 1 knockout to cortical dysfunction, its hippocampal role remained unclear. Here, we demonstrate that PLC $\beta$ 1 in the dentate gyrus functions as a negative modulator of fear memory by regulating neuronal excitability. Conditional deletion of PLC $\beta$ 1 in this region induces hyperexcitability in granule neurons, enhances contextual fear responses, and impairs memory extinction, whereas genetic or optogenetic restoration of PLC $\beta$ 1 attenuates these effects. Temporal activation of PLC $\beta$ 1 specifically during memory encoding, but not retrieval, reduces fear memory formation, suggesting its phase-specific regulatory role. Notably, PLC $\beta$ 1 expression was reduced in PTSD-susceptible mice, and its upregulation alleviated pathological fear, implicating PLC $\beta$ 1 in trauma resilience. Together, these findings uncover a dentate gyrus-specific mechanism by which PLC $\beta$ 1 constrains maladaptive memory encoding through excitability control, positioning it as a potential therapeutic target for stress-related disorders.



**Disclosures:** J. Lee: None.

**Poster**

**PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.06/QQ13

**Topic:** I.08. Learning and Memory

**Support:** DFG grant CA893/17-1  
VolkswagenStiftung Change of Course grant

**Title:** Aperiodicity in mouse CA1 and DG power spectra

**Authors:** \*S. DHINGRA<sup>1</sup>, G. KÜHN<sup>1</sup>, H. EL RASHIDY<sup>1</sup>, F. CALEGARI<sup>2</sup>;  
<sup>2</sup>Ctr. for Regenerative Therapies, <sup>1</sup>TU Dresden, Dresden, Germany

**Abstract:** Rodent hippocampal power spectra comprise of periodic and aperiodic components. The periodic components (brain rhythms) contain information about the behavioral or cognitive state of the animal. The aperiodic components are rarely studied and their functionality is not well understood, though have shown to be correlated with animal's age or the excitation-inhibition ratio of the brain region. Using tetrode electrophysiological signals, we compare the aperiodic activity within mice hippocampal sub-regions, CA1 and dentate gyrus (DG). To study these components, we modified the existing open-source FOOOF toolbox, which was originally optimized for EEG data. Using simulated data, we show that our modifications decrease the error in assessment of the periodic components from 3% to 0.1%. Further, our optimization of FOOOF improved the aperiodic assessment errors by about 50% and were critical in making the first-ever assessments of the aperiodic components in these brain regions. Our results show that the aperiodic parameters in the DG are multi-fold larger than in CA1, revealing higher excitation and longer timescales in CA1 than DG. Our work highlights the subtle differences in electrophysiology field potentials between hippocampal sub-regions, and presents the improvements needed in the existing open-source toolbox to be able to see such differences.

**Disclosures:** S. Dhingra: None. G. Kühn: None. H. El Rashidy: None. F. Calegari: None.

## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.07/QQ14

**Topic:** I.08. Learning and Memory

**Support:** UT Austin Graduate School Continuing Fellowship

**Title:** Correlated Changes in Running Speed and Sublayer-Specific Theta, Beta, and Gamma Oscillations in the Rat Dentate Gyrus

**Authors:** \*J. R. TARANATH<sup>1</sup>, P. G. DEMETROVICH<sup>2</sup>, L. L. COLGIN<sup>3</sup>;  
<sup>1</sup>Electrical and Computer Engin., <sup>2</sup>Neurosci., Univ. of Texas at Austin, Austin, TX; <sup>3</sup>Ctr. for Learning and Memory, The Univ. of Texas At Austin, Austin, TX

**Abstract:** The dentate gyrus (DG) is thought to integrate spatially tuned inputs from the medial entorhinal cortex (MEC) and contextually rich inputs from the lateral entorhinal cortex (LEC). While prior work has established relationships between running speed and oscillatory dynamics (e.g., theta, slow-gamma, and fast-gamma rhythms) in CA1, CA3, and MEC (e.g., *Ahmed and Mehta 2012, Kemere et al. 2013, Long et al. 2014, Zheng et al. 2015*), speed-modulated frequency-specific activity across DG input and output sublayers remains largely unexplored. Here, we investigated how running speed correlates with theta (5-12 Hz), beta (15-25 Hz), slow-gamma (25-55 Hz), and fast-gamma (100-150 Hz) power estimated from local field potentials

(LFPs) in the granule cell layer (GCL), middle molecular layer (MML), and outer molecular layer (OML) of the dorsal DG. LFP depth profiles were recorded using chronically implanted Neuropixels probes in two Long-Evans rats as they ran laps on a circular track. Histology confirmed probe placement in the dorsal DG. Boundaries of the GCL, MML, and OML sublayers were identified by applying cluster-permutation thresholding (*Maris and Oostenveld 2007*) to the characteristic current source density depth profiles during dentate spikes. In preliminary findings, theta, beta, and fast-gamma power increased with running speed across all sublayers. In contrast, slow-gamma power did not appear to similarly increase with running speed. Specific changes in DG oscillations with speed may relate to DG processing that is important for spatial and object learning (*Fernandez-Ruiz et al. 2021*).

**Disclosures:** J.R. Taranath: None. P.G. Demetrovich: None. L.L. Colgin: None.

## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.08/QQ15

**Topic:** I.08. Learning and Memory

**Support:** Funding from Department of Biology & Chemistry, Liberty University

**Title:** Type 1 Diabetes Adversely Negatively Impacts Affective and Cognitive Performance and Neurogenesis in Male and Female Mice

**Authors:** \*M. PINO, IV<sup>1</sup>, S. NELSON<sup>2</sup>, C. YEAGER<sup>4</sup>, R. OOI<sup>1</sup>, A. FROMMACK<sup>1</sup>, K. LONG<sup>3</sup>, K. R. GILLEY<sup>1</sup>;

<sup>1</sup>Dept. of Biol. and Chem., Liberty Univ., Lynchburg, VA; <sup>2</sup>Dept. of Biol. and Chem., Liberty Univ., Nazareth, PA; <sup>3</sup>Dept. of Biol. and Chem., Liberty Univ., Evinston, VA; <sup>4</sup>Dept. of Biol. and Chem., Liberty, Ashburn, VA

**Abstract:** Diabetes affects approximately 8.4 million people worldwide, the prevalence of which is increasing 0.34% annually. Studies of patient populations show that this demographic is ~2x more likely to develop depression and experience cognitive decline associated with dementia. While obesity is a concern for type 2 diabetes (T2D) and in itself correlates with many of these comorbidities, obesity is not frequently associated with type 1 (T1D) but similar reports have been noted. Moreover, clinical reports suggest that affective and cognitive dysregulation is higher in the female population, which is historically under studied preclinically. Thus, the present study aimed to evaluate how hyperglycemia differentially impacted male and female mice. To accomplish this, we used a 2 (sex) x 2 (hyperglycemia) factorial design. T1D was induced in C57BL/6J mice through 5 days of Streptozotocin (STZ) administration, with sex-specific dosing (55 mg/kg/day for males, 70 mg/kg/day for females) to induce hyperglycemia. Behavioral tests, including marble burying (MB) and Barnes maze (BM), were conducted to assess depressive-like behaviors and cognitive impairment. Post-mortem immunohistochemical

staining post-mortem evaluated neurogenesis and astrogliosis in brain tissue. Results revealed that STZ-induced hyperglycemia led to increased aberrant burying behaviors and cognitive dysfunction with deficits observed in MB ( $p = .028$ ) and BM ( $p = .004$ ). Additionally, baseline astrocytic activity differed between males and females ( $p = .029$ ), though this was not impacted by hyperglycemia. Lastly, a sex by hyperglycemia interaction showed a significant reduction to hippocampal neurogenesis ( $p = .038$ ), with STZ females showing a robust reduction in DCX+ cells. For females, reduced neurogenesis strongly negatively correlated with detriments in BM latencies ( $R^2 = .766$ ,  $p = .005$ ), illustrating the relationship to neurobiological changes to behavioral changes. These findings suggest that chronic hyperglycemia negatively impacts brain function, with notable sex-specific differences. Results support the relationship of T1D and its detrimental impacts on neurobiology, cognitive decline, and affective dysregulation, emphasizing the importance of early identification of biomarkers for targeted interventions and highlighting the potential need for sex-specific intervention strategies. Future research in this lab aims to increase sample sizes, assess long-term outcomes, and continue to explore sex differences in this model.

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## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.09/QQ16

**Topic:** I.08. Learning and Memory

**Support:** NASA HERO grant 80NSSC21K0814

**Title:** Complex Galactic Cosmic Radiation Alters Dentate Gyrus Activity and Pattern Separation: Sex-Specific Behavioral Responses and CDDO-EA Countermeasure Effects

**Authors:** \*S. A. O'CONNOR<sup>1,2</sup>, A. MAHAJAN<sup>3</sup>, G. L. BANCROFT<sup>4</sup>, H. A. HAAS<sup>5</sup>, P. K. NARAIN<sup>4</sup>, F. C. KIFFER<sup>6</sup>, A. J. EISCH<sup>7</sup>, S. YUN<sup>8</sup>;

<sup>1</sup>Pathobiology, Univ. of Pennsylvania Sch. of Vet. Med., Philadelphia, PA; <sup>2</sup>Univ. Lab. Animal Resources, <sup>3</sup>Univ. of Pennsylvania, Philadelphia, PA; <sup>4</sup>Children's Hosp. of Philadelphia, Philadelphia, PA; <sup>5</sup>Mount Sinai, New York, NY; <sup>6</sup>The Children's Hosp. of Philadelphia, Philadelphia, PA; <sup>7</sup>Anesth & Crit Care and Neurosci, UPenn & CHOP, Philadelphia, PA;

<sup>8</sup>Anesthesiol. and Critical Care, Children's hospital of Philadelphia, Philadelphia, PA

**Abstract:** Galactic Cosmic Radiation (GCR) threatens astronaut cognitive health during deep space missions. The hippocampus and nucleus accumbens (NAc) are vulnerable to radiation damage and critical for mission-essential cognitive functions. The hippocampal dentate gyrus supports behavioral pattern separation (BPS)—distinguishing similar memories—while the NAc mediates Pavlovian learning crucial for adaptive behavior. Previous simple GCR studies show

inconsistent cognitive effects with emerging evidence of sex dependence in radiation response, making investigation of complex 33-ion GCR exposure essential for developing targeted countermeasures. We hypothesized that whole-body exposure to 33-GCR would produce sex-specific cognitive impairments and that the anti-inflammatory triterpenoid CDDO-EA would differentially mitigate these cognitive deficits based on sex. Here, 5.5 mon-old mature C57BL/6J male and female (n=47/sex) mice received CDDO-EA (4 mg/kg) or Veh for 3 days during IRR exposure, and either Sham IRR or 33-GCR (0.75 Gy, 2hr). Mice then underwent cognitive assessments including the Spontaneous Location Recognition (SLR) task to assess hippocampal-dependent BPS, and a rodent touchscreen based NAs-dependent autoshaping paradigm to evaluate Pavlovian learning. In SLR, 33-GCR impairs BPS (lower discrimination index) under high memory loads, but CDDO-EA reverses the cognitive deficits. This phenomenon is prominently shown in only male mice. In the autoshaping paradigm, males showed no effects of 33-GCR or CDDO-EA on goal-tracking behavior. In females, 33-GCR increased reward collection latency (Days 2 and 5) in both Veh and CDDO-EA groups compared to respective sham controls (Day 1, 2 and 5). During reversal learning, males treated with CDDO-EA made fewer approaches to the lit CS+ across multiple timepoints regardless of GCR treatment, indicating altered learning strategy. However, CDDO-EA does not show a significant effect on cognitive flexibility in female mice. These findings reveal sex-specific treatment effects on cognitive and learning behaviors, where males showed CDDO-EA-related impairments in behavioral flexibility while females demonstrated radiation-induced deficits in reward-related learning, suggesting that radiation and drug treatments affect cognitive processes through distinct, sex-dependent mechanisms. Our results suggest radiation effects differ by brain region and sex, and countermeasures for deep space missions may require sex-specific approaches. This study highlights the importance of examining sex as a biological variable when evaluating potential countermeasures for space radiation.

**Disclosures:** S.A. O'Connor: None. A. Mahajan: None. G.L. Bancroft: None. H.A. Haas: None. P.K. Narain: None. F.C. Kiffer: None. A.J. Eisch: None. S. Yun: None.

## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.10/QQ17

**Topic:** I.08. Learning and Memory

**Support:** NIH ZIAMH002784

**Title:** A novel thermal conflict task to investigate approach-avoidance behavior following ablation of adult neurogenesis

**Authors:** A. SWIERCZ<sup>1</sup>, \*H. A. CAMERON<sup>2</sup>;

<sup>1</sup>Section on Neuroplasticity, <sup>2</sup>NIH, Bethesda, MD

**Abstract:** When difficult decisions must be made, the hippocampus contributes to behavioral conflict resolution by modulating the inhibition of dominant behavioral responses. The dentate gyrus, unique for its ability to produce new neurons into adulthood, plays a key role in this process. But it is currently unclear whether adult neurogenesis is directly involved in difficult decision-making, and which aspects of decision-making are affected by new neurons. Here, we introduce a novel behavioral task to examine the role of adult-born neurons in conflict-based decision-making following the ablation of neurogenesis in adult male rats. Neurogenesis was eliminated by 8 weeks of oral valganciclovir treatment in transgenic Long-Evans rats expressing the herpes simplex virus thymidine kinase (TK) under control of the glial fibrillary acidic protein (GFAP) promoter. Littermates lacking the transgene served as controls. In the cold suppressed feeding task, food-deprived animals were placed in an arena with cold (5°C), neutral (20°C), and warm (35°C) zones. After a single habituation session, food was fixed in the cold zone, compelling animals to choose between feeding and avoiding the aversive cold temperatures. During the habituation phase, when food was absent, rats lacking neurogenesis traveled farther but exhibited similar temperature preferences to wild-type (WT) controls. However, when food was introduced in the cold quadrant, animals lacking adult-born neurons spent less time in the cold zone and exhibited greater latencies to begin eating. These findings indicate that adult-born neurons influence decision making in approach-avoidance conflicts and highlight the cold-suppressed feeding task as a valuable tool for investigating hippocampal neurogenesis. This research was supported by the Intramural Research Program of the NIMH (ZIAMH002784).

**Disclosures:** A. Swiercz: None. H.A. Cameron: None.

## **Poster**

### **PSTR245: Dentate Gyrus**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR245.11/QQ18

**Topic:** I.08. Learning and Memory

**Support:** NIH Grant MH135565  
NIH Grant NS118440  
NIH Grant T32-GM150581

**Title:** Sex as a biological variable in brain activity during contextual fear memory formation, consolidation, and recall.

**Authors:** \*K. O. MCDONALD<sup>1</sup>, T. YU<sup>1</sup>, A. PRABHU<sup>1</sup>, S. J. ATON<sup>2</sup>;

<sup>1</sup>Univ. of Michigan, Ann Arbor, MI; <sup>2</sup>Molecular, Cellular, and Developmental Biol., Univ. of Michigan, Ann Arbor, MI

**Abstract:** Post-learning sleep significantly enhances contextual fear memory task performance in both human and rodent subjects. A large body of research suggests post-learning sleep particularly benefits episodic memory, including contextual fear memory. Multiple brain regions



including the hippocampus, amygdala, and neocortex have been implicated in contextual memory encoding, consolidation, and recall. The specific contribution of these brain regions to each stage of memory formation invites further investigation. Additionally, sex as a biological variable has not been thoroughly investigated with regards to contextual fear memory formation. Some studies show that males perform better than females on contextual memory tasks, while other studies show this effect to be reversed, or non-existent. Thus, a consensus about the precise difference in contextual fear memory performance, and the underlying mechanisms contributing to contextual memory performance, across males and females is inconclusive. Interestingly, some rodent studies have identified variability in cellular activity between males and females in multiple brain regions during contextual fear memory formation. Our present study identifies sex differences in activity of hippocampal subregions as well as the amygdala during contextual fear memory encoding, consolidation, and recall. These findings highlight the need for further investigation into the contribution of different brain regions to memory formation, and how this may vary across sexes.

**Disclosures:** K.O. McDonald: None. T. Yu: None. A. Prabhu: None. S.J. Aton: None.

## **Poster**

### **PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR246.01/QQ19

**Topic:** I.08. Learning and Memory

**Support:** NINDS Grant 15NS118408

**Title:** Gene transcription and mRNA translation are required for long-term excitability changes induced by aversive experience in the feeding neural circuit of *Aplysia*

**Authors:** \*R. MOZZACHIODI, R. MUELLER, M. L. WAINWRIGHT;  
Texas A&M University-Corpus Christi, Corpus Christi, TX

**Abstract:** Long-term memory requires gene transcription followed by mRNA translation to persist over time (Kandel 2001). In *Aplysia*, training with repeated trials of aversive stimuli induces long-term sensitization (LTS) of defensive responses. LTS is sustained, at least in part, by long-term increased excitability (LTIE) of sensory neurons (SNs), which depends on both transcription and translation (Byrne and Hawkins 2015). LTS training also induces long-term feeding suppression (LTFS), which is sustained, at least in part, by long-term decreased excitability (LTDE) of decision-making neuron B51 in the feeding neural circuit (Shields-Johnson et al. 2013). This project examined whether transcription and/or translation were required for B51 LTDE. Actinomycin D (Act-D) and anisomycin (ANI) were utilized to selectively inhibit gene transcription and mRNA translation, respectively. Experiments were conducted using a previously established *in vitro* ganglionic preparation that includes the neural circuits responsible for LTS and LTFS. In this preparation, four trials of electrical stimulation

(each consisting of 10-s, 1 Hz, train of 10 500-ms, 60-Hz, 60-V impulses), delivered to afferent nerves from the body wall (i.e., *in vitro* training), co-induce sensory neuron LTIE and B51 LTDE, compared to untrained controls (Weisz et al. 2017). Treatments consisted of ganglia incubation with artificial seawater (vehicle) containing either ANI (20  $\mu$ M; Castellucci et al. 1986) or Act-D (50  $\mu$ g/ml; Montarolo et al. 1986). SN and B51 excitability were measured before (pre-test) and 24 h after training / no training (post-test). Post/pre percent changes in SN and B51 excitability were compared among six groups of preparations: trained/vehicle, trained/ANI, trained/Act-D, untrained/vehicle, untrained/ANI, untrained/ACT-D. Sensory neuron LTIE was used as a positive control for the effectiveness of ACT-D and ANI. Results indicate that ACT-D and ANI effectively blocked the expression of both SN LTIE (Kruskal-Wallis test followed by Dunn's *post-hoc* comparison) and B51 LTIE (Kruskal-Wallis test followed by Student-Newman-Keuls *post-hoc* comparison). These findings demonstrate that B51 LTDE requires transcription and translation processes for long-term memory formation analogous to those sustaining SN LTIE in the defensive circuits.

**Disclosures:** R. Mozzachiodi: None. R. Mueller: None. M.L. Wainwright: None.

## **Poster**

### **PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR246.02/QQ20

**Topic:** I.08. Learning and Memory

**Support:** NSF Grant IOS-2338915

**Title:** Injury Alters Sensory, Motor, and Integrative Elements Underlying Operant Conditioning in the Medicinal Leech

**Authors:** \*E. DOCKENDORF<sup>1</sup>, B. D. BURRELL<sup>2</sup>;  
<sup>2</sup>Basic Biomed Sci., <sup>1</sup>Univ. of South Dakota, Vermillion, SD

**Abstract:** Pain is a complex experience that has both sensory and affective components. Many current pain assays focus on assessing the sensory component of pain and neglect the emotional component. We used leeches (*Hirudo verbana*, N=8), which are negatively phototactic, to test self-motivated behaviors in relation to injury using an assay that includes a two-choice arena consisting of one dark chamber and one illuminated chamber linked by a connecting section filled with gravel. Animals were placed in the illuminated chamber of the choice arena over five, 180 second trials to cross into the dark chamber. Escape latencies were measured, and it was discovered that as animals completed repeated trials, escape latency decreased showing evidence of operant conditioning, and when retested 2 hours after the last training trial, the learned escape latency was still retained. To test the effect of injury on this learning and memory task, animals (N=14) were injured with a t-pin in their posterior sucker and completed the above training assay. Interestingly, escape latency was reduced in all the trials independent of operant

conditioning and there was no 2-hour retention showing that learning and memory are disrupted when animals are in an injured state. We also measured the mechanosensitivity of the injured animals with Von Frey fibers which showed an increase in sensitivity when the animals were injured. Locomotion of the injured animals differed from non-injured animals as well, but not enough to account for injury induced effects in escape latency. Animals had an increase in exploring the gravel versus the illuminated chamber indicating a change and shift in attentional processes. Finally, injury enhanced negative phototaxis and this appeared to explain the injury-induced decrease in escape latency observed in the injury experiment. As phototaxis recovered, so did learning and memory capabilities. Together, these findings begin to explain the complex set of behaviors that pain constitutes.

**Disclosures:** E. Dockendorf: None. B.D. Burrell: None.

## **Poster**

### **PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR246.03/RR1

**Topic:** I.08. Learning and Memory

**Support:** NIH Grant 2R15MH107892-03

**Title:** Extensive training diminishes forgetting of sensitization in *Aplysia* while narrowing the transcriptional response to learning

**Authors:** C. MCFAUL<sup>1</sup>, D. WITTROCK<sup>2</sup>, \*R. CALIN-JAGEMAN<sup>3</sup>, I. CALIN-JAGEMAN<sup>4</sup>;  
<sup>1</sup>Dominican Univ., Grayslake, IL; <sup>2</sup>Dominican Univ., Elmwood Park, IL; <sup>4</sup>Biol., <sup>3</sup>Dominican Univ., River Forest, IL

**Abstract:** Forgetting remains a key puzzle in the neurobiology of memory. One mysterious aspect of forgetting is its selectivity: most long-term memories are forgotten, becoming less and less accessible over time; extensive training, though, can produce long-term memories that are readily accessible for a lifetime. What is the molecular basis by which some memories become resistant to forgetting? To explore this issue, we have tracked changes in neuronal gene expression following accompanying both long-lasting and forgettable forms of long-term sensitization in *Aplysia californica*. We re-confirmed a robust training effect in this learning paradigm: a 1-day training protocol produced a long-term sensitization memory fully forgotten within 1 week; a 4-day training protocol produced long-term sensitization memory stably expressed for weeks. We then used microarray and qPCR to characterize transcriptional states 1, 5 and 7 days after training. Surprisingly, we found that more extensive training is associated with a narrowing of the transcriptional response: the first round of training produced clear regulation of over 1,000 transcripts, but by the fourth round of training most of these had significantly declined and only 80 transcripts remained clearly regulated. In addition, both forgettable and more stable forms of sensitization produced relatively few lasting transcriptional changes, with

only a few transcripts clearly regulated more than 5 days after training. We are now working to confirm these findings at the single-cell-type level. Our results raise multiple intriguing possibilities about the nature of forgetting, including the possibility that initial learning activates a mixture of both encoding and forgetting processes, with extensive training serving primarily to de-active forgetting.

**Disclosures:** C. McFaul: None. D. Wittrock: None. R. Calin-Jageman: None. I. Calin-Jageman: None.

## **Poster**

### **PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR246.04/RR2

**Topic:** I.08. Learning and Memory

**Support:** DFG grant BR 1892/17-1

**Title:** Motor learning in fruit flies: what happens where and how to improve it

**Authors:** \*B. BREMBS<sup>1</sup>, C. DUCH<sup>2</sup>, R. LYUTOVA-HRISTOVA<sup>1</sup>, A. EHWEINER<sup>1</sup>;  
<sup>1</sup>Univ. Regensburg, Regensburg, Germany; <sup>2</sup>Johannes Gutenberg Univ. of Mainz, Mainz, Germany

**Abstract:** Humans use motor learning to learn how to speak, walk, write or ride a bike. Motor learning is essential also for sports or rehabilitation after stroke or spinal injury. Evidence suggests that all forms of motor learning share an evolutionarily conserved molecular plasticity pathway. We use motor learning in the fruit fly *Drosophila* to study the neurons where the plasticity occurs, the molecular processes mediating the learning as well as various methods to improve motor learning. We operantly trained wild type, mutant and transgenic flies, tethered at a torque meter, in a motor learning task that required them to initiate and maintain turning maneuvers around their vertical body axis (yaw torque). We combined this behavioral experiment with transgenic peptide expression, CRISPR/Cas9-mediated, spatio-temporally controlled gene knock-out, gene overexpression, neuronal activity manipulation and confocal microscopy. Our evidence suggests that a crucial site of plasticity for this type of motor learning resides in the steering motor neurons that control wing beat angles, which, in turn, contribute to generating yaw torque. Our results imply that co-expression of the genes *FoxP* and *aPKC* is required in these steering motor neurons for motor learning to take place. We have also discovered that the foraging gene (a PKG) is necessary for motor learning and are investigating the site of PKG action. This type of motor learning is also highly regulated, such that it can establish a memory quickly or only after sustained training. Part of this regulation involves interactions with other learning systems. We can improve motor learning by genetically manipulating these other learning systems via, e.g. the rutabaga or radish mutants, or via altering

the activity of the neurons mediating the interaction (mushroom body neurons and mushroom body output neurons). Overexpressing aPKC also improves motor learning.

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## **Poster**

### **PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR246.05/RR3

**Topic:** I.08. Learning and Memory

**Support:** NIH Grant R21AA030833

**Title:** Aversive and appetitive associative learning assays and their use in monitoring alcohol dependency in adult *Drosophila*

**Authors:** \*T. WIJESEKERA<sup>1</sup>, H. GEDAMU<sup>3</sup>, A. AMORUSO<sup>2</sup>, S. REDDY<sup>2</sup>, A. VALDEZ<sup>2</sup>, V. MUNOZ<sup>2</sup>, K. CALLAN<sup>2</sup>, E. BERNSTEIN<sup>2</sup>, N. ATKINSON<sup>4</sup>;

<sup>1</sup>Neurosci., <sup>2</sup>Univ. of Texas at Austin, Austin, TX; <sup>3</sup>Univ. of Texas Southwestern Med. Ctr., Dallas, TX; <sup>4</sup>Neurosci., Univ. Of Texas At Austin Inst. For Neurosci., Austin, TX

**Abstract:** We have developed a *Drosophila melanogaster* associative learning assay that is simpler than other canonical fly learning assays. Although simple, it is robust and reliable. It is based on the fact that flies are attracted to light and move towards it. Previously, Le Bourg and Buecher (2002) exploited this behavior to train adults to associate an aversive stimulus with light. The flies learned to act against instinct and moved into the dark. But flies were individually trained and tested in darkness making the assay impractical for general use. We modified this assay to facilitate batch training and testing in a well-lit environment. Furthermore, we showed that the assay works with both aversive and appetitive reinforcement. Flies are collected as pupae and raised in the dark. In the aversive associative-learning assay, batches of adults are exposed to light paired with quinine. A T maze with a light and dark arm is used to test for learning. We have also demonstrated that learning occurs when a food reward is paired with darkness. Once again, trained flies act against instinct and preferentially choose the dark arm in the T maze. These assays are used in a freshman teaching laboratory and even these untrained hands generate significant learning by subjecting flies to only 3 training trials. Flies retain memory of the association for up to one hour. Both assays are being used to probe cognitive alcohol dependence in adults. Previously, with larvae we showed that long-term alcohol exposure could produce functional alcohol dependency. This manifested itself as a need for on-board alcohol for normal levels of associative learning (Robinson et al. 2012). A problem with the larval model is that larval life is extremely short. With the new assay we show that acute alcohol exposure also compromises the adult's capacity to learn. However, chronic alcohol exposure produces flies that learn normally even if alcohol is on board. Importantly, when alcohol is withheld, the capacity to

learn degrades indicating that the flies have become functionally dependent on alcohol for the capacity to learn. The capacity to demonstrate cognitive alcohol dependence in flies provides new avenues for genetically dissecting this phenomenon.

**Disclosures:** T. Wijesekera: None. H. Gedamu: None. A. Amoruso: None. S. Reddy: None. A. Valdez: None. V. Munoz: None. K. Callan: None. E. Bernstein: None. N. Atkinson: None.

## **Poster**

### **PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR246.06/RR4

**Topic:** I.08. Learning and Memory

**Support:** NIH R01 NS121220

**Title:** Sensitization and habituation memories within *Tritonia*'s escape swim network alter efferent neuron intrinsic excitability via different cellular mechanisms

**Authors:** V. MISTRY, E. S. HILL, \*W. N. FROST;  
Ctr. for Brain Function and Repair, Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

**Abstract:** The marine mollusk *Tritonia diomedea*'s ventral/dorsal flexion escape swim is a rhythmic motor program that can undergo two different forms of non-associative learning: sensitization and habituation. This can be observed across various parameters of the swim in both intact animals and in fictive motor programs in the isolated CNS. We have previously identified learning-induced changes in both the intrinsic properties of the swim central pattern generator neurons as well the burst intensity of the ventral phase efferent neurons during the swim motor program. Here, we sought to determine if these changes in efferent neuron burst intensity were due to changes in their intrinsic excitability.

We found that sensitization and habituation both altered efferent neuron excitability, but in different and distinct ways depending on flexion phase. The memory for sensitization, formed after an initial sensitizing stimulus, increased the intrinsic excitability of both dorsal and ventral phase neurons. Repeated stimulation of the same isolated brain, which developed a memory of habituation, only reduced the excitability of ventral phase neurons - dorsal phase neuron excitability returned to naïve levels. Interestingly, these changes in excitability were not correlated with changes in burst intensity in either dorsal or ventral phase neurons, suggesting that changes in burst intensity are primarily driven by changes in pre-synaptic input, not efferent neuron excitability.

As ventral and dorsal phase neuron excitability were not equally affected by sensitization and habituation learning, we then investigated if different cellular mechanisms were involved in changing intrinsic excitability for the different flexion phases during both sensitization and habituation. We found changes in dorsal phase neuron excitability were correlated with changes

in resting membrane potential, while changes in ventral phase neuron excitability were instead correlated with changes in spike frequency adaptation.

The use of multiple cellular mechanisms to alter learning-related neuronal excitability provides a glimpse of how multiple memories may manage to minimize destructive interference when overlapping in the same network space.

**Disclosures:** V. Mistry: None. E.S. Hill: None. W.N. Frost: None.

## **Poster**

### **PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR246.07/RR5

**Topic:** I.08. Learning and Memory

**Support:** NIH Grant 1R01NS118606-01

**Title:** Pairing rejection with a specific food causes a learned decrease of biting responses to the food in *Aplysia*

**Authors:** \*M. LEVY<sup>1</sup>, A. J. SUSSWEIN<sup>2</sup>;

<sup>1</sup>Gonda Brain Res. Ctr., Bar Ilan Univ., Ramat Gan, Israel; <sup>2</sup>Life Sci., Bar-Ilan Univ., Ramat-Gan, Israel

**Abstract:** *Aplysia* produce a number of qualitatively different feeding acts: biting, which transfers food stimulating the lips into the mouth, swallowing, which transfers food into the gut, and rejection, which expels food or non-food objects out of the mouth. Is rejection *per se* aversive? Rejection is classically studied by inducing an animal to swallow a cannula and examining how animals expel the cannula. We examined the possibility that rejection is aversive by pairing rejection of a cannula with food stimulating the lips, and subsequently examining whether the paired food elicits fewer bites (*i.e.*, is less attractive to animals) than does an unpaired food. While *Aplysia* were rejecting a 4 cm cannula, we stimulated the lips with one of two seaweed foods, either *Ulva* or *Gracilaria*. This was repeated 3 times, with 0.5 hours separating rejection bouts. We then measured the number of bites elicited by stimulating the lips with *Ulva* and *Gracilaria* 24 hours later. There was a significant decrease in the number of bites elicited by the food paired with rejection, but not by the unpaired food. A second experiment examined pairing food stimulating the lips with a cannula prepared with a series of holes, and with seaweed placed within the cannula. After the cannula was within the mouth, seawater laced with nutrients released from the food within the cannula leaked out of the holes, thereby stimulating the interior of the mouth, and perhaps being swallowed. Surprisingly, rejection in response to this cannula was more effective than to a cannula without food seeping through holes, in that it took significantly less time to push the cannula out of the mouth. Pairing the cannula with food within it, with the same food also stimulating the lips, also produced a food-specific decrease in bites in response to lip stimulation 24 hours later. These findings suggest that

rejections *per se* are aversive, and therefore pairing food with rejection reduces responses to the food.

**Disclosures:** M. Levy: None. A.J. Susswein: None.

**Poster**

**PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR246.08/RR6

**Topic:** I.08. Learning and Memory

**Title:** Memory formation and avoidance behavior are independently modified by distinct dopamine and serotonin circuits

**Authors:** \*T.-W. CHANG<sup>1</sup>, H. CHIANG<sup>2</sup>;

<sup>1</sup>Natl. Cheng-Kung Univ., Tainan City, Taiwan; <sup>2</sup>Natl. Cheng-Kung Univ., Tainan, Taiwan

**Abstract:** A developed compartmentalized brain organizes distinct regions with special functions to modify animal behaviors distinctly. Although emerging evidence has demonstrated that each specialized brain region interprets external stimuli differently and cooperatively to form a behavior, the detailed cellular regulatory mechanism in regulating different regions to interpret external stimuli remains elusive. In fruit flies, electric shock (E.S.) triggers avoidance behavior and is required to form punishment memory. Our behavioral study showed that two distinct neural circuits, TH-C (dopamine neurons)>Dopamine 1-like receptor 2 (Dop1R2)>Mushroom body  $\alpha'\beta'$  lobes (KC $\alpha'\beta'$ )>MBON- $\alpha'1$  and Trh(S) (serotonin neurons)>5HT-1B>KC $\alpha\beta$ >MBON- $\alpha2$ , are affected by a series of E.S. and modified behavior differently. Although knocking down dopamine and serotonin receptors reverses E.S.-induced memory expression and avoidance damage, respectively, recovering one behavior could not recover the other, suggesting that the two circuits function independently. Live-cell imaging studies showed that KC $\alpha'\beta'$  and KC $\alpha\beta$  interpret a series E.S. differently. KC $\alpha'\beta'$  focuses on overall neural activity, while KC $\alpha\beta$  focuses on distinguishing individual stimulation. Our study reveals that different compartmentalized brain domains could function independently via different neural circuits to reflect external stimulation.

**Disclosures:** T. Chang: None. H. Chiang: None.

**Poster**

**PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR246.09/RR7



**Topic:** I.08. Learning and Memory

**Support:** BT/HRD-NBA-NWB/38/2019-20(Y1)

**Title:** One memory to go please - Release of extracellular vesicles from neurons act as modes of transfer of long-term associative memory from one *Caenorhabditis elegans* to another and their possible role in *Caenorhabditis briggsae*

**Authors:** \***M. BHAR**<sup>1</sup>, T. NANDI<sup>2</sup>, H. NARAYANAN<sup>3</sup>, K. BABU<sup>4</sup>;

<sup>1</sup>Ctr. for Neurosci., Indian institute of Sci., Bangalore, India; <sup>2</sup>Ctr. for Neurosci., Indian Inst. of Sci., Bangalore, India; <sup>3</sup>Univ. Konstanz, Konstanz, Germany; <sup>4</sup>Biol. sciences, Ctr. For Neurosci., Bangalore, India

**Abstract:** Native preference and behaviour in organisms can be modified through learning. In this study, we have looked at long-term associative memory (LTAM) in *Caenorhabditis elegans* by training them using two cues - the native chemoattractant isoamyl alcohol (IAA), and heat as the repulsive cue. This training paradigm results in the formation of LTAM, observed in the form of loss of attraction from IAA due to aversive learning, which can last for up to 24 hours. Here, we report a novel mechanism by which *C. elegans* due to aversive training, release specific factors onto the plate, through environmentally released extracellular vesicles (EVs) from the IL2 neurons. Removal of animals from these plates causes them to lose this memory despite undergoing aversive training. These factors released through EVs can further be taken up by other *C. elegans* (naïve as well as known memory-defective mutants) and induce aversive memory in these animals without any prior training. We report that mutant animals defective in biogenesis or release of EVs from the IL2 neurons are defective in LTAM. We also report that the nature of the factors released through EVs is specific to the olfactory odour used as the training cue and changes according to the olfactory cue. To further investigate the underlying molecular mechanism, we have performed liquid chromatography mass spectroscopy (LC-MS) to identify the factors released by animals due to training. This has led us to discover a candidate group of small molecules, exposure to which is enough to elicit the phenotypic response of aversion to the training cue as described above. To understand the evolutionary significance of this phenomenon, we investigated its existence in *Caenorhabditis briggsae*. We report that *C. briggsae* shows LTAM using our training paradigm. This memory can also be transferred from one *C. briggsae* to another as well as in an inter-species fashion between *C. briggsae* and *C. elegans*. However, interestingly, the removal of *C. briggsae* from their training plates did not cause them to forget, unlike *C. elegans*. This study uncovers a new avenue of communication and signaling in *C. elegans* and its nervous system and reports a previously unknown role for the IL2 neurons as well.

**Disclosures:** M. Bhar: None. T. Nandi: None. H. Narayanan: None. K. Babu: None.

**Poster**

**PSTR246: Learning and Memory in Invertebrates**

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**Program #/Poster #:** PSTR246.10/RR8

**Topic:** I.08. Learning and Memory

**Support:** PAPIIT IN225925  
PAPIME PE305125

**Title:** Environmental cues in place localization

**Authors:** \*N. TRUJILLO GUTIÉRREZ<sup>1</sup>, F. SÁNCHEZ<sup>1</sup>, J. F. VERGARA-OVALLE<sup>3</sup>, D. B. PAZ-TREJO<sup>1</sup>, H. SANCHEZ-CASTILLO<sup>2</sup>;

<sup>2</sup>Psychobiology and Neurosciences, <sup>1</sup>Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; <sup>3</sup>Biochem., UNAM, Cd de Mexico, Mexico

**Abstract:** To prevent predation and to ensure their survival, the octopuses use dens for protection and isolation. There's a wide variety of objects that may be used as shelter such as shells, rocks and even human objects. Once the octopus has found a safe den, it tends to spend most of the day inside it, and, only when there's food shortage or it's not considered safe anymore the animals abandon it to search for a new one. Octopuses, in safe conditions, can stay up to three months in the same den. Because of this behavior, if the octopus is used to leave its den to forage the territory nearby, how does it find its way back to their den? The main goal of this research was to study the role of the environmental (visual) cues in the localization of the den in octopus of two weeks old. We used an experimental box divided into three sections, the middle section was empty and each side wall was decorated with different plants, behind each wall there was either a den (a shell) or nothing. On the first day we allowed the octopus to explore the new space and find the den by its own. Once the octopus chose the shell as a den, we proceed to take it out of the shell and place it back on the center of the box. We hypothesized that the octopus would use the plants as visual cues in order to swim to the correct location where its den was. Our results showed that the visual cues were not important in the decision-making process when the octopus attempted to return to its den. However, we noticed that other cognitive elements such as spatial orientation, muscle memory and interoception were crucial elements for the octopus den localization.

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**Poster**

**PSTR246: Learning and Memory in Invertebrates**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR246.11/RR9

**Topic:** I.08. Learning and Memory

**Support:** DGAPA-PAPIIT IN 225 925  
DGAPA-PAPIME PE 305 125

**Title:** Agonistic behavior of two different crayfish species

**Authors:** \*H. SANCHEZ-CASTILLO<sup>1</sup>, N. TRUJILLO GUTIÉRREZ<sup>1</sup>, F. SÁNCHEZ-FLORES<sup>2</sup>, J. F. VERGARA-OVALLE<sup>3</sup>, D. B. PAZ-TREJO<sup>1</sup>;

<sup>1</sup>Univ. Nacional Autónoma de México, Mexico City, Mexico; <sup>2</sup>Univ. Nacional Autónoma de México, Mexico City, Mexico; <sup>3</sup>Biochem., UNAM, Cd de México, Mexico

**Abstract:** Aggressive behaviors play an important role in both intra and interspecific interactions and could be directly related to species survival, which is a trait, commonly observed in invasive species. Although aggression plays a role as an adaptive function, in some contexts it could be disruptive, being perceived as violence or harassment in social organisms that depend on grouping to survive, such as fishes, rats, mice, chimpanzees, humans. The opportunity to compare different species closely related could show essential mechanisms and components that play a role in aggressive behavior. We observed two species of the *Procambarus* genus *P. clarkii* and *P. alleni*. These are two very similar species regarding their maintenance conditions, size, behavior and diets, making them ideal for comparative behavioral studies. Four subjects were evaluated, (two subjects of each species), we used two arenas for agonistic confrontations with one hour of duration. At the beginning, the animals were introduced at the same time and videotaped the whole hour for posterior analysis. We found that *P. alleni* showed a higher frequency in aggressive/ dominance behaviors without interference of context or subjects' sizes. Our results suggest that the aggression-related mechanisms of the *P. alleni* may have different behavioral and neurobiological approaches that allow them to increase their survival over the other kinds of *Procambarus* in hostile conditions.

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**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.01/RR10

**Topic:** I.09. Spatial Navigation

**Support:** ERC Grant H2020

**Title:** Voltage imaging of CA1 pyramidal cells and SST+ interneurons reveals stability and plasticity mechanisms of spatial firing

**Authors:** \*R. KIPPER<sup>1</sup>, Y. MELAMED<sup>2</sup>, Q. YANG<sup>2</sup>, S. BAROR-SEBBAN<sup>2</sup>, Y. ADAM<sup>2</sup>, G. SHTURM<sup>2</sup>;

<sup>1</sup>The Edmond and Lily Safra Ctr. for Brain Sci., <sup>2</sup>The Hebrew Univ. of Jerusalem, Jerusalem, Israel

**Abstract:** Hippocampal place cells (PCs) play an important role in spatial coding and episodic memory. PCs' representations are dynamically modulated upon transitioning to novel environments (global remapping), but also slowly change with repeated exposure to familiar spaces (representational drift). To gain insights into the mechanistic basis for this unique balance between plasticity and stability at different parts of the CA1 microcircuit, we used high-speed voltage imaging to longitudinally record the subthreshold and spiking activity of pyramidal neurons (PNs) and somatostatin-positive (SST) interneurons in the mouse CA1 during virtual reality navigation. As expected, a fraction of the cells from both populations showed spatial tuning, but a large fraction of SST cells was either tuned to the running speed or showed uniform high firing activity across the environment. Intracellular recordings from both cell types revealed distinct subthreshold features underlying their spatial firing: PN place fields showed increased theta power and an asymmetric ramp-like depolarization, while SSTs exhibited symmetric depolarization with no increase in theta. Longitudinal recordings across weeks demonstrated representational drifts in both populations, even though SSTs exhibited remarkably stable firing and subthreshold properties. Finally, an abrupt transition to a novel environment induced remapping in spatially tuned cells from both populations, accompanied by a transient increase in SST activity and reduction in PN activity. Together, these results shed light on the distinct features of SSTs and PNs activity during spatial navigation, and in response to context switching. They suggest that increased dendritic inhibition might play a role in memory encoding during novel experiences, potentially by sparsening the PN code.

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## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.02/RR11

**Topic:** I.09. Spatial Navigation

**Support:** German Science Foundation (DFG)  
NeuroCure Excellence Cluster - EXC 2049 / project number: 390688087  
CRC/TRR 384 "IN-CODE"

**Title:** Optogenetic control of mitochondria within parvalbumin-positive interneurons impairs spatial properties in the CA1 region of the hippocampus

**Authors:** \***R. PATEL**<sup>1,2,3</sup>, **J. WALTHER**<sup>2</sup>, **C. ELGUETA**<sup>4</sup>, **J. VIEROCK**<sup>2</sup>, **M. HABERL**<sup>2,5</sup>, **S. VIANA DA SILVA**<sup>1,3,5</sup>;

<sup>1</sup>German Ctr. for Neurodegenerative Dis., Berlin, Germany; <sup>2</sup>Charité – Universitätsmedizin Berlin, Berlin, Germany; <sup>3</sup>Einstein Ctr. for Neurosci., Berlin, Germany; <sup>4</sup>Freiburg Univ., Freiburg Im Breisgau, Germany; <sup>5</sup>Bernstein Ctr. for Computat. Neurosci. Berlin, Berlin, Germany

**Abstract:** Parvalbumin-positive (PV+) interneurons within the hippocampus are crucial for allowing and maintaining spatial memory functions that are otherwise impaired in neurodegenerative diseases. To maintain such an extensive control, PV+ interneurons require a high energy demand, which necessitates highly functional mitochondria to supply the cells with ATP efficiently. Previous studies have shown mitochondrial dysfunction is present within the hippocampus (HPC) in early cases of Alzheimer's Disease (AD), even preceding the major pathological hallmarks: amyloid-beta plaques, tau aggregation, and memory impairments. Optogenetic tools have been instrumental in discovering and understanding the function of neurons within multiple different brain networks. Recently developed tools have expanded their use to allow for light-control of intracellular organelles, such as mitochondria. To understand how the mitochondria of PV+ interneurons contribute to learning and memory processes regulated by the hippocampal CA1 circuit, we utilized a previously developed optogenetic construct, mitoChR2, which targets the inner mitochondrial membrane. In the presence of light, the channel opens and causes a disruption of the proton motive force that drives ATP production, thus decreasing the quantity of ATP produced (Tkatch et al., 2017). Using stereotaxic delivery of a Cre-dependent adeno-associated vector encoding mitoChR2, combined with performing in vivo electrophysiological recordings in the dorsal CA1 of the hippocampus in freely moving PV-Cre mice, we discovered that optogenetic stimulation of mitoChR2 reduced the firing activity of both interneurons and pyramidal cells within the CA1. These changes consequently altered the spatial properties of place cells during exploration of a familiar environment, as well as during a spatial memory task. Our findings emphasize the importance of mitochondria in learning and memory mechanisms, and suggest mitochondria be considered for potential therapeutic targets for the treatment of AD.

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## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR247.03/RR12

**Topic:** I.09. Spatial Navigation

**Support:** NIH Grant R56NS129556 (CG, FC, AS)  
NSF Grant IOS2011998 (AS)  
Smith Family Awards Program for Excellence in Biomedical Research (CG)

**Title:** Spillover-activation of metabotropic glutamate receptors refines cognitive maps of spatial information

**Authors:** \*M. A. PETROCCIONE<sup>1</sup>, M. MELONE<sup>2</sup>, T. RATHWELL<sup>3</sup>, C. GRIENBERGER<sup>4</sup>, F. CONTI<sup>5</sup>, A. SCIMEMI<sup>6</sup>;

<sup>1</sup>Biol., Univ. At Albany - SUNY, Albany, NY; <sup>2</sup>Exptl. and Clin. Med., Univ. Politecnica delle Marche, Ancona, Italy; <sup>3</sup>State Univ. of New York, Univ. of Albany, Albany, NY; <sup>4</sup>Dept. of Biol., Brandeis Univ., Waltham, MA; <sup>5</sup>Univ. Politecnica della Marche, Ancona, Italy; <sup>6</sup>Biol., SUNY Albany, Albany, NY

**Abstract:** Group III metabotropic glutamate receptors (mGluRIII) are widely expressed at excitatory and inhibitory synapses throughout the mammalian brain. However, in the hippocampus, prior slice physiology studies in area CA1 have shown that mGluRIII activation suppresses glutamate and GABA release onto GABAergic interneurons, but not onto pyramidal cells. Our findings indicate that this apparent target-specific modulation of GABAergic transmission is an artifact of the non-physiological extracellular calcium concentrations that were historically used in acute brain slice preparations. When the extracellular calcium concentration approximates that of cerebrospinal fluid, mGluRIII activation suppresses GABA release from synapses onto *both* pyramidal cells and interneurons, while still selectively reducing glutamatergic input onto interneurons. This calcium-sensitive presynaptic modulation of inhibitory input onto pyramidal cells is due to shifts in the size of the readily releasable pool of vesicles, which are mediated via the competing activity of protein kinase A and calcineurin on the phosphorylation state of the vesicle-associated proteins, synapsins. In awake, behaving mice, pharmacological blockade of mGluRIII activation in CA1 decreases inhibition onto CA1 pyramidal cells, causing place cells to fire more frequently outside of their place field, suggesting that mGluRIII contributes to controlling disinhibition onto CA1 pyramidal cells. Together, these findings revise the prevailing view of mGluRIII function, revealing a broader role for mGluRIII in shaping synaptic transmission and the encoding of spatial information within the hippocampus.

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## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

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**Program #/Poster #:** PSTR247.04/RR13

**Topic:** I.09. Spatial Navigation

**Support:** NSF Grant IIS 2342866

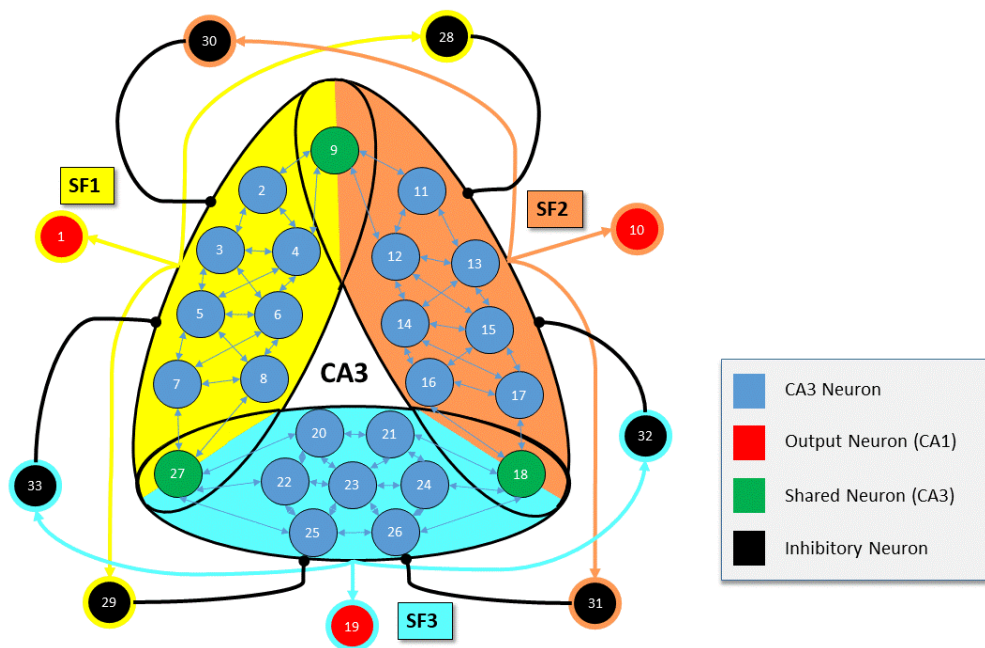
**Title:** Mechanisms of Emergence of Dorsal CA1 Place Cells Multi-fields in Megaspaces

**Authors:** C. CAPOZELLA<sup>1</sup>, \*J.-M. FELLOUS<sup>2</sup>;

<sup>1</sup>Univ. of Arizona, Tucson, AZ; <sup>2</sup>UCSD, La Jolla, CA

**Abstract:** Within the hippocampus, place cells exhibit location-specific firing. Regions where place cells have high firing activity are referred to as place fields. Rodent dorsal CA1 place cells have been studied previously in small environments. In small mazes, these cells form one and

rarely two place fields. Recently, place field activity has been studied in megaspace, a large environment about an order of magnitude larger than traditional mazes. In this space, rats navigate mostly away from maze boundaries. Dorsal CA1 place cells in this larger space commonly feature multiple place fields of different sizes (one to eight subfields). Why does a single cell in CA1 fire at different locations in megaspace? We hypothesize that CA1 subfields are ‘bound’ to each other by neural activity in the presynaptic CA3. The binding between subfields was evidenced by partial synchrony of cells in each field. To assess this hypothesis, we used the NEURON biophysical simulator to create ‘bound’ CA1 place fields from CA3 activity and alter the connectivity matrix to simulate different conditions. We developed a model consisting of groups of CA3 neurons to evaluate two theories in three environment sizes (small, medium, and megaspace). The first theory relies on binding mediated by CA3 neurons that are shared between fields and propagate activity from one subfield to another, achieving CA1 multi-field activity. The second theory relies on the patterned activity of inhibitory neurons projecting onto the CA3 neurons. In this model, CA1 multi-field activity emerges as a function of an inhibitory decrease in activity. Our results make specific predictions about the possible CA3 to CA1 mechanisms that yield multi-field properties in megaspace and may provide support for new animal experiments to further test our hypotheses.



**Disclosures:** C. Capozella: None. J. Fellous: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.05/RR14

**Topic:** I.09. Spatial Navigation

**Title:** Minimum grid cell inputs required for place cell firing

**Authors:** \*A. AGGARWAL;

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**Abstract: Goal:** To find the minimal number of grid cells required to replicate place cell firing.

**Methods:** To test our hypothesis, we took CA3 place cell firing data from the Moser lab [1] of 342 different place cells from 8 animals in 11 different rooms. We took one of the 100+ cells that fired in a single room. In the first experiment, we created 1500 grid cell firing patterns with spatial firing frequency of 28 cm, 1-60 degrees and 0-25 phases based on [2] in Matlab.

Connection weights between these grid cells and the place cell were learned with backpropagation algorithm (100 trials of 10000 iterations each) to achieve the place cell firing observed in lab. In subsequent experiments, we tested different combinations of grid cells - different number of phases (from 6 to 25) with all directions, contiguous and non-contiguous phases; different number of directions for 7 phases (every 2<sup>nd</sup>, 4<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 20<sup>th</sup>, 30<sup>th</sup>); and using directions/phases that have positive weight values and those that have negative weight values only (in trials with 1500 grid cells). The corresponding weights were analyzed - using histograms of all weights phase-wise; compared different weights from trials in which place cell patterns were learnt versus those in which they were not learnt. **Results:** Any of these 3 combinations - all 1500 grid cells, any 7 phases with all directions of grid cells, first 7 phases with every 15<sup>th</sup> direction replicated the place cell firing correctly. Weights corresponding to these trials exhibited sinusoidal pattern. Trials with grid cells of less than 7 phases but all 60 directions or fewer than 4 directions but 7 phases or non-contiguous directions/phases (where weights were above zero in trials with all 1500 grid cells) failed to replicate the place cell firing patterns. For the cases where place cell firing was learned, the connection weights from a particular grid cell don't change with different combination of phase/direction. **Conclusion:** In this work, we observed that a minimum of 28 grid cells with single frequency, 7 phases and 4 directions, if they are periodic and contiguous, are sufficient to replicate the place cell firing pattern in a single room out of the 11 rooms that the animal moved in. Connection weights between grid and place cell stay the same irrespective of combination of grid cell phase/direction. **References** 1. Alme et. al., 2014, "Place cells in the hippocampus: Eleven maps for eleven rooms", PNAS:111(52), 18428-18435. 2. Lian, Burkitt, 2021, "Learning an Efficient Hippocampal Place Map from Entorhinal Inputs Using Non-Negative Sparse Coding", eNeuro, 8 (4) ENEURO.0557-20.2021.

**Disclosures:** A. Aggarwal: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.06/RR15

**Topic:** I.09. Spatial Navigation



**Support:** NSF Grant IIS 2342866

**Title:** Causality in Replay: Detecting Effective Connectivity from Spike Trains

**Authors:** \*M. YOUSUF<sup>1</sup>, L. PAGNIER<sup>1</sup>, M. CHERTKOV<sup>1</sup>, J.-M. FELLOUS<sup>2</sup>;

<sup>1</sup>Mathematics, Univ. of Arizona, Tucson, AZ; <sup>2</sup>Inst. for Neural Computation, UCSD, La Jolla, CA

**Abstract:** Hippocampal replay is characterized by the reactivation of population-wide neural sequences during sleep and rest. These reactivated patterns often resemble neural activity observed during prior wakefulness while the animal performs a task. In rodents engaged in spatial navigation, hippocampal replay frequently appears as recurring sequences of place cell firings, where each place field corresponds to a specific spatial location. Replay generation plays a crucial role in memory consolidation and in the long-term retrieval and decoding of stored memories. Replay episodes often embed information about the causal firing structure within neural networks, providing an experimentally accessible window into the manner in which memories are neurally represented. We investigate the relationship between replay and effective connectivity by simulating activity in a network of CA3 place cells, as observed in rats during navigation. Using the NEURON simulation environment, we implement a single-compartment, multi-current pyramidal cell network. The network employs biologically realistic AMPA and NMDA synapses for synaptic transmission and includes in vivo-like stochastic excitatory and inhibitory background noise. Synaptic conductance is scaled using a connectivity matrix, which we manipulate to introduce controlled causal influences among neuron subgroups. To detect effective connectivity, we introduce a decision-flow generative model inspired by stochastic optimal control/transport. This model uses a Markov Decision Process framework to extract transition probabilities that implicitly reflect causal influences in the data. We compare its performance to that of the established DirectLiNGAM causal discovery algorithm, cross-correlation analysis, and a basic spike-counting method, benchmarking each against the ground-truth connectivity matrix. We evaluate the robustness and degradation profiles of all methods across variations in key network parameters, including sparsity, synaptic strength, network size, and sample count. Our findings demonstrate how identifying neurons involved in replay, along with the order in which replay episodes propagate, illuminates the role of place cells in spatial navigation and offers insights into learning and decision-making in large and complex environments.

**Disclosures:** M. Yousuf: None. L. Pagnier: None. M. Chertkov: None. J. Fellous: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.07/RR16

**Topic:** I.09. Spatial Navigation

**Support:** NSF 2318065

**Title:** Uncovering the dynamics of hippocampal replay using state-space modeling

**Authors:** \*Z. WU<sup>1</sup>, X. WEI<sup>2</sup>;

<sup>2</sup>Dept. of Neurosci., <sup>1</sup>The Univ. of Texas at Austin, Austin, TX

**Abstract:** The hippocampus and associated brain regions exhibit replay activity during sharp-wave ripples (SWRs). These replay events are believed to be important in learning, memory, and planning. They may also have important implications in developing learning algorithms in artificial intelligence. Surprisingly, how to identify replay events from SWRs and characterize their structure remains an ongoing debate. Most existing methods rely on restrictive assumptions, by detecting replay activities based on the sequential order of spike trains or the posterior probability decoded from a Bayesian framework. More recent studies have turned to state-space models, which provide more flexible characterizations of replay dynamics. However, how these models relate to classic methods in detecting replays and how well they can capture the properties of replay in the brain remain poorly understood.

We have developed a general and interpretable state-space model based on drift-diffusion process. The prevalence of drift-diffusion dynamics captures whether an SWR contains a spatially coherent trajectory. Moreover, drift and diffusion parameters in our model directly reflect speed and quality of the replayed trajectory. Applications of our framework to experimental data provide new insights into several open questions in the study of hippocampal replay. Specifically, we found that, while many SWRs are stationary, a distinct subset exhibits drift-diffusion dynamics. The drift parameter within this subset suggests that replay trajectories progress in an accelerated manner compared to real movement trajectories of rats. Our analysis also revealed that the spatio-temporal relation of replayed trajectories deviates from random walk. Furthermore, by applying multiple shuffling strategies, we examined the presence of preplays and found that the results depend on the specific types of shuffling procedures used. We expect our method to be broadly applicable in studying the structure of replay activity in the brain.

**Disclosures:** Z. Wu: None. X. Wei: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.08/RR17

**Topic:** I.09. Spatial Navigation

**Support:** HHMI  
NIH Grant 5R01NS057819

**Title:** Impaired long-term stability of hippocampal memory representations in a mouse model of Rett syndrome

**Authors:** \*T. R. ZHANG<sup>1</sup>, H. Y. ZOGHBI<sup>2</sup>, J. C. MAGEE<sup>3</sup>, S. VAIDYA<sup>4</sup>;

<sup>1</sup>Dept. of Neurosci., Baylor Col. of Med., Houston, TX; <sup>2</sup>Mol. and Human Genet., Baylor Col. of Medicine/HHMI, Houston, TX; <sup>3</sup>Neurosci., HHMI, Houston, TX; <sup>4</sup>Baylor Col. of Medicine/Howard Hughes Med. Inst., Houston, TX

**Abstract:** Rett syndrome (RTT), caused by loss-of-function mutations in the *MECP2* gene, is a devastating neurodevelopmental disorder that leads to severe learning and memory deficits. A mouse model of RTT (female *Mecp2*<sup>+/-</sup> mice) retains normal hippocampal contextual memory on a short timescale (20-60 minutes) but exhibits profound memory deficits on a longer timescale (one day). How alterations in the hippocampal neuronal activity underlie these memory deficits across extended timescales remains unclear. To examine this issue, we performed *in vivo* two-photon calcium imaging to record the activity of the same population of hippocampal CA1 pyramidal neurons for seven consecutive days in RTT and wild-type (WT) mice engaged in a spatial learning task. Behaviorally, spatial memory-guided behavior was impaired in RTT mice, as reflected by diminished anticipatory licking. Tracking the dynamics of place cells (PCs), we observed that, in WT mice, a population of hippocampal CA1 place cells (PCs) with enhanced stability across days emerged with repeated task experience, thus progressively stabilizing CA1 representations. However, with similar task experience, RTT mice exhibited a larger ensemble of PCs that were more susceptible to shifts in their place field (PF) locations, consequently impairing the experience-dependent stabilization of CA1 representations. Further analyses showed that the initial formation and subsequent re-establishment of PF activity were primarily driven by behavioral timescale synaptic plasticity (BTSP) in WT and RTT mice. However, in RTT mice, we found that BTSP events were more frequently associated with PCs at new PF locations compared to PCs at the same location in WT mice, arguably affecting long-term stability of CA1 representations. These results reveal a novel mechanism by which altered synaptic plasticity in the hippocampal circuits contributes to unstable spatial representations and memory deficits in RTT mice.

**Disclosures:** T.R. Zhang: None. H.Y. Zoghbi: None. J.C. Magee: None. S. Vaidya: None.

## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.09/RR18

**Topic:** I.09. Spatial Navigation

**Support:** NIMH R01MH117964

**Title:** Sleep loss impairs the specificity of future place field representations and mimics a de novo learning state in the hippocampus

**Authors:** \*N. R. KINSKY<sup>1</sup>, B. K. GIRI<sup>2</sup>, K. DIBA<sup>3</sup>;

<sup>2</sup>Anesthesiol., <sup>3</sup>Dept of Anesthesiol., <sup>1</sup>Univ. of Michigan, Ann Arbor, MI

**Abstract:** Sleep following learning is crucial for long-term memory consolidation. Previous work from our lab has shown that hippocampal cells that fire together during a novel waking experience continue to reactivate together for 5-8 hours during post-experience rest/sleep, and that sleep loss significantly diminishes the strength and duration of reactivation. Other recent work from our lab demonstrated that the extent to which single neurons fire together with place cell ensembles during natural sleep predicts the location of those cells' future firing locations. Based on these results, we hypothesized that reactivation during post-learning sleep/rest supports the long-term stability of place cell firing. To casually test this hypothesis, we performed chronic high-density electrophysiological recordings in region CA1 of the dorsal hippocampus of two male and two female Long Evans rats before, during, and after exposure to a novel linear track (MAZE). Following track exposure, rats underwent sleep deprivation (SD, n=5 sessions) via gentle handling for five hours or were allowed to sleep naturally (NSD, n=3 sessions), and were re-introduced to the same track (reMAZE) 9 hours later. Contrary to our hypothesis, we found no difference in mean MAZE-reMAZE place field correlations between NSD and SD sessions, suggesting that sleep does not impact the stability of newly formed fields. We next probed how sleep deprivation impacted other place field firing properties. First, we observed reduced minute-to-minute reliability of place field firing following SD. Second, we found that population-level spatial tunings following SD remained broad during both MAZE and reMAZE but sharpened during reMAZE sessions following NSD. In agreement, we found that the peak firing rate of both the primary and secondary fields for each place cell increased following sleep deprivation. Third, interneuron firing rates decreased significantly during reMAZE following SD only, indicating that sleep loss might impair spatial tuning specificity by limiting the ability of interneurons to suppress out-of-field firing. Finally, preliminary analyses found that population burst event rates increased following SD, suggesting that reactivation levels might likewise increase following sleep loss. These results indicate that sleep loss pushes the hippocampus to a state where *de novo* learning occurs even in a previously experienced environment.

**Disclosures:** N.R. Kinsky: None. B.K. Giri: None. K. Diba: None.

## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.10/SS1

**Topic:** I.09. Spatial Navigation

**Support:** NIH Grant R01NS115233  
NIH Grant R01MH139216

**Title:** Data-driven discovery of updating populational and neuronal representations in the hippocampus

**Authors:** \*D. D. LUO<sup>1,2</sup>, C. KEMERE<sup>2</sup>;

<sup>1</sup>Rice Neuroengineering Initiative, Houston, TX; <sup>2</sup>Electrical and Computer Engin., Rice Univ., Houston, TX

**Abstract:** Our memories and understanding of the world keep on updating as time goes by and more experiences are accumulated. The hippocampus, a key player in memory and spatial navigation, is found to be modulated by many factors, including both position and time. In this study, we investigate how the hippocampus encodes multiple episodes of similar experiences in novel contexts, specifically, how its representations of the same context are updated over learning and extensive explorations at both the populational and single-neuron levels.

To avoid being biased by prior assumptions on the encoded external variables, we use the extended Poisson Gaussian-process latent variable model (eP-GPLVM) to find the low-dimensional latent neural structure from high-dimensional spike trains. This nonparametric model only assumes smooth mapping functions and smooth temporal latent dynamics, suitable for data-driven discoveries of variable tuning and unsupervised decoding.

When applied to hippocampal neural data recorded from rats exploring a novel open field over four sessions with varied environmental setups, the model reveals the evolution of underlying neural structure: animal positions appeared to be smoothly encoded on a planar manifold that gradually translates as experience accumulates.

Since the neural population coactivation pattern differences are the main factor separating datapoints in the latent space, locations in the latent space indicate different repeated neural cofiring patterns. Leveraging the statistical nature and tractable neuronal tuning of this model, the latent tuning of individual neurons can be delineated, whose latent place field(s) were determined by their preferred cofiring populations at that specific moment. Given that animal positions are encoded in the latent space in this dataset, tracking the change of neuronal latent tunings across time offers an unsupervised way to reveal groups of neurons with different spatial tuning stability.

**Disclosures:** D.D. Luo: None. C. Kemere: None.

## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.11/SS2

**Topic:** I.09. Spatial Navigation

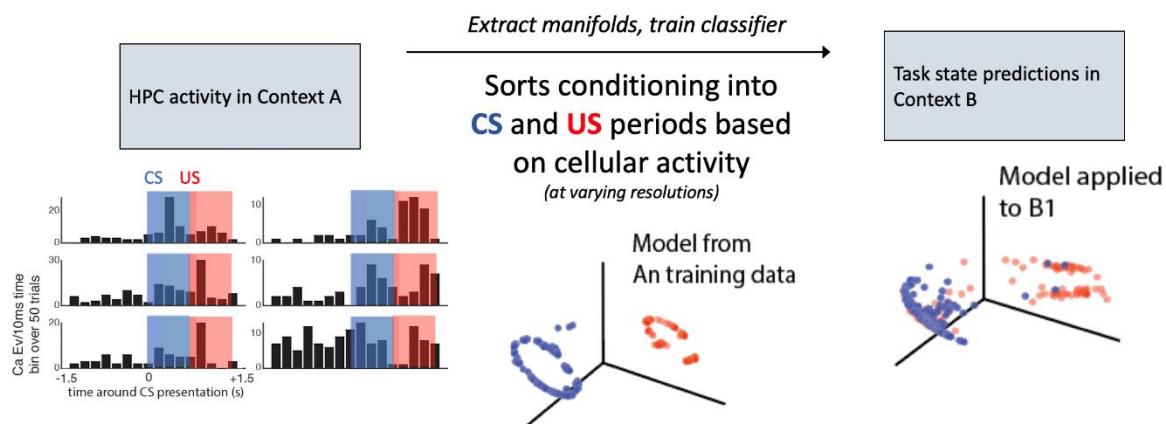
**Support:** BRAIN Initiative K99/R00 K99MH135062  
NIA R01 R37AG008796/AG/NIA  
NINDS R01 R01 NS113804/NS/NINDS

**Title:** A universal hippocampal memory code across animals and environments

**Authors:** \*H. S. WIRTSHAFTER<sup>1</sup>, S. A. SOLLA<sup>2</sup>, J. F. DISTERHOFT<sup>3</sup>;

<sup>1</sup>Northwestern Univ., CHICAGO, IL; <sup>2</sup>Neurosci., Northwestern Univ., Chicago, IL; <sup>3</sup>Neurosci., Northwestern Univ. - Chicago, Chicago, IL

**Abstract:** How learning generalizes across contexts is a fundamental question in neuroscience, with broad implications for adaptive behavior and cognition. The hippocampus (HPC) plays a key role in contextual learning, but HPC cells exhibit place-specific activity that reorganizes, or ‘remaps’ across environments, raising the question of how stable, task-relevant representations can be preserved. Here, we used calcium imaging to monitor hippocampal neuron activity as rats performed a conditioning task across multiple spatial contexts. We asked whether hippocampal neurons, which encode both spatial locations and task-relevant features, could maintain stable representations of the task despite remapping of spatial codes. To assess representational consistency, we applied dimensionality reduction and machine learning to construct manifold embeddings of population-level HPC activity. We found that task-related neural representations remained stable across different environments, even as spatial representations shifted. Moreover, these representations exhibited similar geometric structure not only across contexts within individual animals, but also across different animals, suggesting the presence of a shared neural syntax for associative learning in the hippocampus. These findings bridge a critical gap between memory and navigation research, revealing how stable cognitive representations emerge from dynamic spatial codes. Additionally, they provide new insight into conserved hippocampal encoding strategies, with potential relevance for understanding flexible memory, learning, and their disruption in neuropsychiatric disorders.



**Disclosures:** H.S. Wirtshafter: None. S.A. Solla: None. J.F. Disterhoft: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.12/SS3

**Topic:** I.09. Spatial Navigation

**Support:** National Medical Research Council (MOH-000962)

**Title:** Non-linear mixed selectivity in neurons in the non-human primate hippocampus

**Authors:** R. HERIKSTAD<sup>1</sup>, H. TAN<sup>1</sup>, P. NG<sup>2</sup>, C. B. OWENS<sup>1</sup>, C. LIBEDINSKY<sup>1</sup>, \*S.-C. YEN<sup>1</sup>;

<sup>1</sup>The N.1 Inst. for Hlth., <sup>2</sup>Natl. Univ. of Singapore, Singapore, Singapore

**Abstract:** Mixed selectivity has been reported to be more prevalent in the non-human primate (NHP) hippocampus than selectivity for single variables. We characterised the prevalence of NHP place, view, and head direction selectivity during a virtual goal-directed navigation task and dissociated the confounding influences of each spatial variable in mixed-selective cells. A randomly chosen target poster was shown as a cue lasting 1 second at the start of each trial. The cue poster then reduced in size and remained at the top of the screen as a hint, while the animal was given a 25 second time limit to navigate to the correct target location. This allowed us to investigate selectivity to non-spatial variables when the animal was looking at the cue or the hint, and spatial variables when the animal was navigating the virtual environment. Out of 346 cells, we found place selectivity in 32 cells (9.2%), view selectivity in 33 cells (9.5%), head-direction selectivity in 37 cells (10.7%). 32 out of 49 cells (65.3%) exhibited mixed selectivity. Only 3 pure place cells, 7 pure spatial view cells, and 7 pure head direction cells were identified. 29 out of the 32 cells (90.6%) that exhibited mixed selectivity exhibited conjunctive activity. Most of the spatially selective and view selective (29 out of 32 spatially selective, 24 out of 33 view selective) cells also encoded non-spatial information, i.e. information about the poster identity when viewing the cue or the hint, but these were often different from the selectivity for poster identity in the virtual environment. In order to understand how multiple pieces of information like place and view could be encoded conjunctively in a population of neurons, we created recurrent neural networks to solve a working memory task in which multiple pieces of information (abstracted as angular variables for simplicity) needed to be encoded and reported back at the end of the trial. When these inputs were presented with no statistical correlations between them, which would be similar to situations where all view positions were visible from all locations within an environment, there was a good mix of neurons that exhibited linear and non-linear mixed-selectivity. However, when the inputs were no longer independent, which would be similar to situations where certain view positions were only visible from certain locations within an environment, there was a greater proportion of neurons that exhibited non-linear mixed-selectivity. These findings provide insights into the high occurrence of neurons exhibiting non-linear mixed-selectivity in our recordings.

**Disclosures:** R. Herikstad: None. H. Tan: None. P. Ng: None. C.B. Owens: None. C. Libedinsky: None. S. Yen: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.13/SS4

**Topic:** I.09. Spatial Navigation

**Support:** NIH U01NS128664

**Title:** Model-free action selection requires hippocampal state representations in a spatial decision task

**Authors:** \*S. WANG<sup>1</sup>, R. GRGURICH<sup>2</sup>, P. GOLSHANI<sup>4</sup>, H. T. BLAIR, IV<sup>3</sup>;

<sup>2</sup>Psychology, <sup>3</sup>Dept Psychology, <sup>1</sup>UCLA, Los Angeles, CA; <sup>4</sup>UCLA Dept. of Neurol., Los Angeles, CA

**Abstract:** Model-based (goal-directed) decision strategies select actions by simulating future outcomes using internal models, making them sensitive to outcome revaluation. Model-free (habitual) strategies select actions based on cached action values and are typically insensitive to such revaluation. Model-based behavior involves frontal cortex and hippocampus (HPC), while model-free control is thought to depend on dorsal striatum. Here, we present evidence that model-free decisions require HPC under circumstances where action values are linked to hippocampal state representations. Rats performed a navigation task on a plus maze surrounded by a 2x2 m square track (田); automatic doors controlled access to maze segments. At the start of each trial, rats navigated from the maze center to either a west (W) or east (E) choice point. At each choice location, the correct response (left or right turn) led to a preferred reward (evaporated milk), while the opposite response led to plain water. Notably, the correct direction to obtain milk was opposite at the two locations (e.g., W: left→milk; E: right→milk), requiring rats to localize themselves within the broader maze environment to choose correctly. Rats were assigned to one of three groups: 1) Path Integration (PI), trained in darkness without cues, 2) Tactile Cue (TC), trained in darkness with distinct floor textures at W vs. E choice points, or 3) Beacon Cue (BC), trained with LED lights next to milk wells. After achieving ≥90% accuracy for choosing milk, rats were water-deprived. Some then received negative feedback training (NF: standard maze session followed by milk vs. water preference test), others underwent incentive learning (IL: preference test only). PI-NF and TC-NF rats flexibly shifted to choosing water during NF training, but BC-NF rats did not (despite preferring water off-maze), exhibiting inflexible choice behavior akin to reversal learning failure. Following rehydration and retraining, rats were again water deprived for a revaluation test (extinction session on the maze followed by off-maze preference test). NF-trained rats chose the empty water well (goal-directed) while IL-trained rats chose the milk well (habitual). Notably, HPC inactivation disrupted performance in PI-IL and TX-IL (but not BC-IL) rats that behaved habitually, reducing their choice accuracy. This finding suggests that even in rats for which action selection is habitual, HPC may still be necessary to represent the current latent state and thus to access cached action values upon which model-free decisions depend.

**Disclosures:** S. Wang: None. R. Grgurich: None. P. Golshani: None. H.T. Blair: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H



**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.14/SS5

**Topic:** I.09. Spatial Navigation

**Support:** U01NS128664

**Title:** Path integration is necessary for flexible goal-directed navigation

**Authors:** S. WANG<sup>1</sup>, D. AHARONI<sup>2</sup>, \*H. T. BLAIR<sup>3</sup>;  
<sup>1</sup>Psychology, <sup>2</sup>Dept. of Neurol., <sup>3</sup>UCLA, Los Angeles, CA

**Abstract:** When navigating, animals may use cognitive maps to infer novel routes to a destination (model-based navigation), or they may rely on rigid route-following strategies that cause them to habitually retrace familiar paths (habit-driven navigation). Here we present evidence that model-based navigation depends upon Pavlovian learning mechanisms and requires path integration, whereas model-free navigation depends upon Instrumental learning mechanisms and requires spatial landmark cues. Three groups of rats were trained to navigate to a fixed goal corner from two central start arms on a plus maze embedded within a 2×2 m square track (田). To isolate different spatial strategies, the PI group was trained in darkness without landmark cues (forcing reliance on path integration); the VC group experienced rigid trial-wise rotation of the goal and visual cue (disrupting path integration and forcing reliance on visual landmarks); and the PI+VC group was trained with both stable self-motion cues and consistent visual landmarks. All groups reached acquisition criterion at similar rates. After training, rats received a Novel Route probe in which they had to reach the familiar goal from an untrained starting location. All groups succeeded except VC rats deprived of path integration during the probe, who failed to discover the novel route, suggesting they relied on a habitual, route-based navigation strategy. By contrast, PI and PI+VC rats solved the novel route and thereby showed flexible model-based behavior. In a subsequent Reversal probe, the goal location was switched, reversing the correct start-response mappings from the two originally trained starting locations. VC rats failed to reverse within 64 trials, further supporting their reliance on a habit-based strategy. PI rats reversed rapidly, likely by re-anchoring their internal spatial map to the new goal location (i.e., resetting their path integrator). PI+VC rats also succeeded but required more trials, possibly because the visual cue had to be decoupled from the cognitive map before it could be mentally rotated and anchored to the new goal location. Alternatively, PI+VC rats may have formed a new Pavlovian association between the new goal corner and reward, thereby acquiring a second model-based policy within the original (unrotated) spatial reference frame. To distinguish between these latter two possibilities, ongoing studies are using a wireless version of the UCLA v4 miniscope to record head-direction cell populations in retrosplenial cortex, and thereby infer the cognitive map's orientation during detour probes and reversal learning.

**Disclosures:** S. Wang: None. D. Aharoni: None. H.T. Blair: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.15/SS6

**Topic:** I.09. Spatial Navigation

**Title:** Action-specific spatial coding in the medial entorhinal cortex of flying bats

**Authors:** \*G. GINOSAR<sup>1</sup>, D. MCNAMEE<sup>2</sup>, L. LAS<sup>1</sup>, N. ULANOVSKY<sup>1</sup>;

<sup>1</sup>Weizmann Inst. of Sci., Rehovot, Israel; <sup>2</sup>Neurosci., Champalimaud Res., Lisboa, Portugal

**Abstract:** Medial entorhinal cortex (MEC) contains a diversity of spatially-tuned cells, typically studied during random foraging. However, real-world navigation involves behaviors that go beyond random-foraging - yet the impact of these actions and behaviors on spatial coding remains poorly understood. Here we recorded from the MEC of flying bats as they either randomly-foraged for food, or engaged in two distinct directed actions: takeoff and landing. Bats flew in a large flight-room containing between 6-11 identical rest-platforms at various locations. Neurons in the deep layers of MEC exhibited sparse action-specific spatial coding: They fired at a specific location (near a platform), but only during a specific action - landing or takeoff - and not when flying through the same location during random-foraging. Inspired by reinforcement-learning theory, we showed that these position×action neurons may provide a low-dimensional compositional basis for constructing a flexible, action-dependent spatial map - which addresses a longstanding gap in the reinforcement-learning perspective on spatial cognition.

**Disclosures:** G. Ginosar: None. D. McNamee: None. L. Las: None. N. Ulanovsky: None.

## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.16/SS7

**Topic:** I.09. Spatial Navigation

**Title:** Hippocampal neural manifolds in freely flying bats on a remote oceanic island

**Authors:** \*Y. WASERMAN??, S. RAY, S. PALGI, L. LAS, N. ULANOVSKY;

Weizmann Inst. of Sci., Rehovot, Israel

**Abstract:** The brain has evolved to support complex behavior adapted to the challenges of the natural world. However, most of our understanding of neural coding - both at the level of single neurons and neuronal populations - has come from studies of animals that are head-fixed or moving in simple laboratory settings, far removed from natural behaviors. Here, we present the first study of a neuronal population manifold in any brain area or species during complex, natural, unconstrained behavior outdoors. Using high-precision GPS tracking and wireless electrophysiology, we simultaneously recorded from over 150 hippocampal CA1 neurons in bats freely flying outdoors as they navigated a remote, uninhabited island. Neural recordings began

with each animal's first exploration of this novel environment and continued across multiple days. We will present our findings characterizing the neural manifold in the mammalian hippocampus during real-world navigation outdoors.

**Disclosures:** Y. Wasserman?: None. S. Ray: None. S. Palgi: None. L. Las: None. N. Ulanovsky: None.

## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.17/SS8

**Topic:** I.09. Spatial Navigation

**Title:** Hippocampal neurons encode identities of agents encountered during navigation

**Authors:** \*E. FARBER, S. RAY, S. PALGI, O. SPIEGEL, L. LAS, N. ULANOVSKY;  
Brain Sci., Weizmann Inst. of Sci., Rehovot, Israel

**Abstract:** The hippocampus is well known for mapping space. It contains place cells - neurons that represent the self-position of the individual, which are thought to be important for navigation. Navigation often involves awareness of other individuals that are encountered - either of the same species (conspecifics) or from other species (heterospecifics). While recent work has shown that hippocampal place cells modulate their firing rate based on the identity of conspecifics (Ray et al. Science, 2025), it remains unclear how place cells respond to individuals of other species. To address this, we performed wireless recordings of single neurons in the dorsal hippocampal area CA1 of wild-caught bats as they flew in a familiar environment towards a specific target. We compared how place cells changed their firing pattern when the bats flew towards an empty target or flew along the same trajectories towards an agent - where the agent could be an inanimate object, a conspecific, or a heterospecific - and it could have different identities. Our findings suggest that the majority of recorded neurons modulated their spatial tuning based on the navigational context - mostly via changing their firing rates (rate remapping). Distinct sets of neurons responded to either conspecifics, heterospecifics or objects, with some neurons overlapping in their selectivity. Within a category, neurons also encoded the specific identity of the agent. We also analyzed the neural population and could decode the category and identity of the agent. Altogether, our preliminary findings indicate that hippocampal neurons encode social context during navigation by incorporating information about agent species and identity - in addition to the classical spatial representation.

**Disclosures:** E. Farber: None. S. Ray: None. S. Palgi: None. O. Spiegel: None. L. Las: None. N. Ulanovsky: None.

## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.18/SS9

**Topic:** I.09. Spatial Navigation

**Title:** Head-direction cells as a neural compass in bats navigating outdoors on a remote oceanic island

**Authors:** \*S. PALGI<sup>1</sup>, S. RAY<sup>1</sup>, S. R. MAIMON<sup>1</sup>, Y. WASERMAN<sup>??1</sup>, T. ELIAV<sup>1,2</sup>, A. TUVAL<sup>1</sup>, C. COHEN<sup>1</sup>, L. LAS<sup>1</sup>, N. ULANOVSKY<sup>1</sup>;

<sup>1</sup>Weizmann Inst. of Sci., Rehovot, Israel; <sup>2</sup>MPI for Biol. Intelligence, Seewiesen, Germany

**Abstract:** Animals and humans rely on their navigation skills to survive. However, spatial neurons in the brain's "navigation circuit" were never studied under real-world conditions. Here, we conducted the first electrophysiological study of spatial neurons in the wild. We recorded head-direction cells from the presubiculum of bats that were flying unconstrained and navigated outdoors on a remote oceanic island. We found that these neurons represented the bat's orientation stably across the island's entire geographical scale, and irrespective of the dynamics of the moon and the Milky Way. The directional tuning stabilized over several nights from the first exposure. These results imply that head-direction cells can serve as a learned, reliable neural compass for real-world navigation - highlighting the power of taking neuroscience out to the wild.

**Disclosures:** S. Palgi: None. S. Ray: None. S.R. Maimon: None. Y. Waserman??: None. T. Eliav: None. A. Tuval: None. C. Cohen: None. L. Las: None. N. Ulanovsky: None.

**Poster**

**PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.19/SS10

**Topic:** I.09. Spatial Navigation

**Support:** ERC-CoG – NATURAL\_BAT\_NAV  
DFG – SFB 1372  
NIH R01 – NS121413  
BSF 2020806  
DE-SC0022042  
ISF 1829/23

**Title:** Sparse-to-dense coding transformation between hippocampal subregions CA3 and CA1 in very large environments

**Authors:** \*S. R. MAIMON<sup>1</sup>, T. ELIAV<sup>1</sup>, J. ALJADEFF<sup>2</sup>, Y. GRONICH<sup>3</sup>, N. FINGER<sup>4</sup>, K. EVELAND<sup>4</sup>, C. F. MOSS<sup>4</sup>, L. LAS<sup>1</sup>, N. ULANOVSKY<sup>1</sup>;

<sup>1</sup>Weizmann Inst. of Sci., Rehovot, Israel; <sup>2</sup>Section of Neurobiology, Div. of Biol. Sci., UC San Diego, La Jolla, CA; <sup>3</sup>Edmond and Lily Safra Ctr. for Brain Sci., Hebrew Univ. of Jerusalem, Jerusalem, Israel; <sup>4</sup>Dept. of Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

**Abstract:** The mammalian hippocampus is crucial for spatial memory and navigation. It contains place-cells, spatially-selective neurons which reside in two distinct hippocampal subregions with dramatically-different anatomical connectivity: areas CA1 and CA3. Prior studies have found surprisingly similar spatial coding between CA1 and CA3 place-cells, consisting mainly of single place-fields with similar field sizes. This raises a conundrum: Why would two consecutive subregions with major structural differences exhibit identical neural coding? Importantly, all prior comparisons of CA1 and CA3 were conducted in animals navigating in relatively small arenas. Here, we hypothesized that different neural coding will be revealed in large naturalistic environments — and we tested this hypothesis by simultaneously recording from CA1 and CA3 neurons in bats flying in very large environments: flight-tunnels up to 200-meters long. We discovered dramatically distinct neuronal coding between CA1 and CA3 place-cells: While CA1 neurons exhibited dense spatial coding, consisting of multiple place-fields, CA3 neurons exhibited ultra sparse spatial coding, consisting predominantly of single place-fields. Despite the striking difference in the number of place-fields, the sizes of individual place-fields were remarkably similar between the two subregions, across 5 different environment sizes. Using a neural-network model, we showed that the sparse-to-dense architecture can facilitate fast learning of new spatial maps in the hippocampus. Additionally, we found that in a large multi-compartment environment, place-cells in both subregions exhibited strong contextual effects of trajectory history (‘retrospective coding’), which could last for >100 meters and >12 seconds. Together, these results demonstrate long-range contextual effects in the hippocampus, and a surprising functional difference in neural-coding between hippocampal subregions — highlighting the importance of using large experimental setups with naturalistic scales when studying the brain.

**Disclosures:** S.R. Maimon: None. T. Eliav: None. J. Aljadeff: None. Y. Gronich: None. N. Finger: None. K. Eveland: None. C.F. Moss: None. L. Las: None. N. Ulanovsky: None.

## **Poster**

### **PSTR247: Place Cells, Mechanisms, and Navigation Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR247.20/SS11

**Topic:** I.09. Spatial Navigation

**Title:** Hippocampal spatial codes in bats navigating outdoors on a remote oceanic island

**Authors:** \*S. RAY, S. PALGI, Y. WASERMAN??., S. R. MAIMON, T. ELIAV, A. TUVAL, C. COHEN, L. LAS, N. ULANOVSKY;  
Weizmann Inst. of Sci., Rehovot, Israel

**Abstract:** Animal brains and their behaviours have evolved in the natural world - to enable them to meet the challenges they face during their daily lives. However, our understanding of how the brain represents the world, stems from experiments performed in simple laboratory settings. While laboratory-based experiments reveal what neurons can encode, they leave the fundamental question unexplored - how does the brain actually represent the real world? To tackle this challenge, we performed the first single-unit neural recordings from freely flying bats as they navigated outdoors on a remote oceanic island. To achieve this, we developed a wireless neural-logger with an integrated high-precision GPS and altimeter - allowing us to record electrophysiological activity from hundreds of single neurons simultaneously, together with the bat's position and altitude in the real world. We tracked the bats from the first day they explored this novel geographical area, and recorded their navigation behaviour and dorsal hippocampal CA1 place cells as they explored the island over multiple days. We found that as the bats navigated the island, hippocampal neurons exhibited place fields in three-dimensions (3D), with different neurons representing different locations - as expected from place cells. Single place cells had multiple place-fields in 3D. The unconstrained bats flew at different altitudes over the island, and different place-fields of single neurons often encoded distinct altitudes. Here we will describe our findings - providing the first view on spatial coding in the mammalian hippocampus during real-world navigation outdoors.

**Disclosures:** S. Ray: None. S. Palgi: None. Y. Waserman??: None. S.R. Maimon: None. T. Eliav: None. A. Tuval: None. C. Cohen: None. L. Las: None. N. Ulanovsky: None.

## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.01/SS12

**Topic:** I.10. Human Learning and Cognition

**Title:** Replay as a mechanism to update the hippocampal predictive map

**Authors:** \*A. BAZARJANI, P. PIRAY;  
Dept. of Psychology, USC, Los Angeles, CA

**Abstract:** It has long been known that the hippocampus “replays” sequences of place cells representing specific trajectories, without the animal physically occupying those locations. However, the computational nature of hippocampal replay has been a long-discussed topic with many different theories. Reinforcement learning has provided a mathematical framework for interpreting replay, with the dominant theory positioning it as a goal-directed planning

mechanism. While influential, this theory falls short of explaining emerging data on hippocampal replay. More broadly, it remains unclear whether and how replay supports a cognitive map that is useful not only for planning but also for generalization when the environment changes, for example after the introduction of a new barrier or goal. Here, we suggest that replay primarily serves to update the hippocampal cognitive map. Viewing this map as a predictive one, such as the successor representation that encodes expected occupancy across states, our recent work has outlined how the brain efficiently updates the map when encountering new goals or barriers by reusing previous computations. We propose that hippocampal replay provides a mechanism for this updating by prioritizing the replay of memories that are most consequential for modifying the cognitive map. We demonstrate that this formulation produces updates to the predictive map that closely resemble replay patterns observed across diverse neural experiments. Our computational model simulates various experimental paradigms from the neuroscience literature involving reward-based navigation in rodents in maze environments. Crucially, our model extends beyond traditional planning models of replay by reproducing recent temporal findings showing that forward replay systematically precedes reverse replay, something the previous models failed to capture. Furthermore, our framework provides a unifying explanation for seemingly contradictory results from two separate T-maze experiments, where replay exhibits goal-directed behavior in one setting but not the other. Taken together, our results unify seemingly disparate replay results and provide compelling evidence for observing replay not as a planning mechanism, but to update the hippocampus' predictive map.

**Disclosures:** A. Bazarjani: None. P. Piray: None.

## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.02/TT1

**Topic:** I.10. Human Learning and Cognition

**Support:** shanahan foundation fellowship

**Title:** Segmenting High-Dimensional Neural Population Activity into Interpretable Behavioral Units

**Authors:** \*S. WU<sup>1</sup>, R. P. RAO<sup>2</sup>;

<sup>1</sup>Allen Inst. and the Univ. of Washington, Seattle, WA; <sup>2</sup>Paul G. Allen Sch. for Computer Sci. and Engin., Univ. of Washington, Seattle, WA

**Abstract:** How information propagates across brain areas and how they relate to behavior and task-related variables has been a key question for neuroscience and interpretable machine learning alike. In this ongoing project, we propose that neural population activity mirrors regularities in the environment or the task. We provide evidence for this hypothesis, known as

the Reflection Hypothesis, extending previous work in machine learning models to biological neural population activity. This hypothesis, which complements sparse coding and Bayesian brain theories, suggests structural correspondences between neural dynamics and external task patterns. We leverage the concept of chunking to segment high-dimensional neural population dynamics into interpretable units that reflect recurring patterns in behavior or the task environment. We demonstrate that this method, in combination with Rastermap (Stringer et al. 2025), extracts recurring neural population activity as chunks, which enables the study of interactions between brain areas at the population level. Our study paves the way for future approaches that integrate interpretability methods in machine learning for uncovering neural circuit interactions with mechanistic and computational models.

**Disclosures:** S. Wu: None. R.P. Rao: None.

## Poster

### PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.03/TT2

**Topic:** I.10. Human Learning and Cognition

**Support:** R01NS119468  
R01AG088306

**Title:** Humans adaptively discount successor representations when navigating graph-structured spaces

**Authors:** \*A. BOORAS<sup>1</sup>, T. KAPOGIANIS<sup>4,2</sup>, E. R. CHRASTIL<sup>3</sup>, A. BORNSTEIN<sup>5</sup>;  
<sup>2</sup>Neurobio. and Behavior, <sup>3</sup>Neurobio. & Behavior, <sup>1</sup>Univ. of California, Irvine, Irvine, CA;  
<sup>4</sup>UCSD, Irvine, CA, ; <sup>5</sup>Universtiy of California, Irvine, Irvine, CA

**Abstract:** People form internal representations or *cognitive graphs* that reflect local associations within the environment. One possible mechanism by which people learn cognitive graphs is the *successor representation*, which encodes each state of the environment in terms of the discounted future occupancy of other states<sup>1,2</sup>. The *discount factor* quantifies how far in the future such associations extend. A recent study found that individuals' navigation decisions in a community-structured state space can be well-approximated by a successor representation<sup>3</sup>. However, it is still unknown whether individuals optimally adapt their discount factor to capture the characteristic long- and short-range regularities of different graph forms. Here, we examined behavior as individuals explored several kinds of graph-structured state spaces. Participants learned stimulus-stimulus associations by viewing groups of images (nodes) representing potential paths (edges), and selecting one to traverse. This selection triggered the presentation of another image group. Participants were not told the underlying graph structure. In the test phase, participants were asked to find the path from a given starting node to a target node. Accuracy and



efficiency were measured for each choice. Participants navigated four types of graphs: grid/lattice, community-structured, community-structured with additional ‘bridge’ nodes separating each community, and unstructured/random. We used simulations to determine the optimal discount factor for each structure, and compared these to the factors obtained by fitting each participant’s responses. We then examined how discount factors changed in response to graph type. Participants whose discount factors adapted most from the least structured (random) to the most (bridges), could be said to be the most flexible in their representation of the current environment. Indeed, individuals whose discount factors adapted to a greater degree between random and bridge (i.e. greater difference) also had better average performance ( $r=.31$ ,  $p=.031$ ). Additionally, the greater the difference in fitted discount factors between the most (bridge) and second-most (community) structured graph, the better was average performance ( $r=.49$ ,  $p<.001$ ). In other words, people who changed their discount factor to better align with the optimal discount of a particular graph had better navigation. These results suggest that people may adaptively discount based on environmental structure.

<sup>1</sup>Dayan, P. Neural Comput. (1993) <sup>2</sup>Stachenfeld, K. L., Botvinick, M. M. & Gershman, S. J. Nat. Neurosci. (2017) <sup>3</sup>Wientjes, S. & Holroyd, C. B. PLoS Comput. Biol. (2024)

**Disclosures:** A. Booras: None. E.R. Chrastil: None. A. Bornstein: None.

## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.04/TT3

**Topic:** I.10. Human Learning and Cognition

**Support:** IBS-R015-D1 (IBS)  
RS-2023-00211018

**Title:** Human Analogical Reasoning Violates Geometric Assumptions of Vector-Based Models

**Authors:** \*S. SAMRA<sup>1</sup>, S. M. YOO<sup>2</sup>;

<sup>1</sup>Ctr. for Neurosci. Imaging Res., Suwon-si, Korea, Republic of; <sup>2</sup>Neurosci., Univ. of Rochester, Minneapolis, MN

**Abstract:** Analogical reasoning is identifying a relationship between two things and mapping those relationships onto novel pairs. Computational approaches often model analogical reasoning using vector-based word embeddings, where relational similarity is represented geometrically. A key example is the parallelogram model, which assumes that relationships between word pairs can be captured as vector differences. These models assume that relational similarity follows geometric constraints such as the triangle inequality, which in mathematics means that the sum of any two sides of a triangle is greater than or equal to the third side. In analogy, if A is similar to B and B to C, then A should be similar to C. However, such models assume a pair's similarity

is stable and context-independent. We hypothesized that when there are two types of relationships for one pair, it would lead to context-dependent violations of the triangle inequality and challenge the assumptions of vector-based models. To investigate this, we developed an analogy task where participants revealed four masked images one-by-one through fixation and then rated the similarity between pairs. We created 18 questions, each of four pairs of related items labeled A, B, C, and D. Pairs AB, AC, and BC share the same relation; pair AD has a different relation, while pairs BD and CD have no meaningful relation. This configuration formed two comparison triangles: one with AB, AC, and BC, and another with AB, AD, and BD. This enabled us to test whether relational similarity judgments followed the triangle inequality within a consistent relation, and whether that pattern was violated when a different relation was introduced. We found that the triangle inequality was often violated in the mixed-relation triangle, but preserved in the consistent-relation triangle. These findings suggest that human relational similarity judgments are context-sensitive. To determine if this was unique to human reasoning, we tested the same questions on large language models. The results showed fewer violations and more geometry-consistent patterns, reflecting the underlying assumptions of vector-based representations.

**Disclosures:** S. Samra: None. S.M. Yoo: None.

## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.05/TT4

**Topic:** I.10. Human Learning and Cognition

**Support:** Postdoctoral Fellowship-SECIHTI to CJMR  
UNAM-PAPIIT: IN221324  
CONACYT: 263377

**Title:** Changes in brain oscillations across spatial-emotional learning in healthy men

**Authors:** \*C. J. MONTES RODRIGUEZ<sup>1,2</sup>, S. TRUJILLO<sup>2</sup>, Z. MUNOZ-TORRES<sup>2,3</sup>, M. MULLER<sup>1</sup>;

<sup>1</sup>Ctr. de Investigación en Ciencias, UAEM, Cuernavaca, Mexico; <sup>2</sup>Ctr. de Ciencias de la Complejidad, UNAM, Mexico City, Mexico; <sup>3</sup>Facultad de Psicología, UNAM, Mexico City, Mexico

**Abstract:** Spatial computation has been linked to theta rhythm in rodents (4-12 Hz), however, there is a discussion about theta rhythm boundaries in humans. Human theta rhythm has two components, around 3-4 Hz (related to retrieval) and 4-8 Hz. To explore the neuronal oscillations during spatial-emotional processing, we designed a spatial-emotional task that can be retrieved by bimodal sensory cues (visual and auditory) and recorded the spontaneous activity between

learning sessions, in adult healthy men. Task. An association was established between an emotional image (negative or neutral), a paired sound and one out of four positions in the screen (place), during 3 learning sessions. After 20 min of resting with closed eyes, a short-term memory (STM) test was performed using sounds as cues. Memory accuracy consisted in remembering the place on the screen where images were shown. Electroencephalographic activity based on the 10-20 system was analyzed during spontaneous activity between learning sessions. Participants returned to the laboratory the next day in the morning to perform two long term memory (LTM) tests, using both visual and auditory cues in a counterbalanced manner. Behavioral data show that participants learned the task with 73% of accuracy at STM test (cue-sound). After a night of sleep 72% of accuracy was observed at LTM. Interestingly, when retrieval was evoked by the image the accuracy level was 85%. We observed a 20% improvement during the STM test (retrieved by sounds). Negative stimulus increased accuracy when the image was used as cue during retrieval but not when the cue was the sound. Finally, preliminary data of the EEG analysis shows that spontaneous activity before learning has less power of delta-theta oscillations compared to spontaneous activity after learning. On the other hand, the power of alfa-beta oscillations decreases after learning. Our data suggests that delta-theta oscillation is participating in spatial-emotional memory consolidation and retrieval, supporting the role of delta-theta oscillations on spatial computation in humans.

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## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.06/TT5

**Topic:** I.10. Human Learning and Cognition

**Title:** Investigating prefrontal cortical involvement in human spatial pattern separation using functional near-infrared spectroscopy

**Authors:** \*M. I. GOMEZ, F. DE LAURENTIIS, S. JOYCE, S. J. WONG-GOODRICH; Psychology and Neurosci., Iona Univ., New Rochelle, NY

**Abstract:** Pattern separation (PS) is a computational process in the brain that supports memory accuracy by differentiating between highly similar inputs or events. While extensive research has implicated the dentate gyrus in the hippocampus as a key region for PS, less is understood about the specific contributions of the prefrontal cortex (PFC) to this process (Amer & Davachi, 2023), particularly human spatial PS. Here, we used functional near-infrared spectroscopy (fNIRS; BIOPAC Systems, Inc.) to measure PFC activity, based on concentration changes in oxygenated hemoglobin (O2Hb), during a spatial mnemonic discrimination task. A sample of 25 young adults (8 males, 17 females) completed a spatial memory task with 72 trials, each consisting of a

sample and choice phase where participants judged whether a grey circle appearing on a computer screen during the choice phase was either the same or different as the location of the original grey circle that appeared in the sample phase. The circle's spatial location in the choice phase was either 0, 0.5, 1, 1.5, or 2 cm to the left or right of the circle's original location in the sample phase. Thus, compared to larger separations (1.5 cm and 2 cm), smaller separations (0.5 cm and 1 cm) between the sample and choice phase locations place greater demands on PS due to the increased potential for memory interference. To control for response biases, task performance was analyzed using standard signal detection theory procedures to yield a discrimination sensitivity measure ( $d'$ ) for small and large separation conditions. Participants wore a 16 channel fNIRS headband device to capture changes in O2Hb concentrations in the PFC during choice phases (memory retrieval), compared to a baseline during which participants viewed a fixation cross for 10 seconds. As predicted, participants performed better on large compared to small separation trials, with significantly higher  $d'$  scores for the large spatial separation condition,  $t(24) = 5.07$ ,  $p < .001$ . Analyses also revealed a significant increase in overall PFC O2Hb concentration changes for both small and large separation conditions,  $ps < .001$ , with the largest increase observed in the large separation condition,  $t(24) = 4.48$ ,  $p < .001$ . These findings suggest an increase in PFC activity, measured through fNIRS, associated with memory retrieval during a spatial PS task. A higher increase in PFC activity in the large separation condition may be due to the possibility that during small separation trials, the spatial locations may have appeared similar enough that participants more often judged the location as unchanged, reducing the demands on prefrontal cognitive control.

**Disclosures:** M.I. Gomez: None. F. De Laurentiis: None. S. Joyce: None. S.J. Wong-Goodrich: None.

## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.07/TT6

**Topic:** I.10. Human Learning and Cognition

**Title:** Contextual Novelty shapes mesolimbic responses to memory success signals

**Authors:** \*Y. LIU<sup>1</sup>, I. C. BALLARD<sup>2</sup>, J. B. HUTCHINSON<sup>1</sup>, V. P. MURTY<sup>1</sup>;

<sup>1</sup>Dept. of Psychology, Univ. of Oregon, Eugene, OR; <sup>2</sup>Psychology Dept., UC Riverside, Riverside, CA

**Abstract:** Prior work shows that successfully retrieving information is intrinsically rewarding, often engaging regions within the mesolimbic dopamine system, including the ventral tegmental area (VTA) and nucleus accumbens (NAcc). Mesolimbic signaling is sensitive to contextual features, such that novelty has been shown to boost reward signals. However, the influence of contextual novelty on reward-related retrieval signals has yet to be characterized. To address

this, we leverage the high-resolution Natural Scenes Dataset (NSD), in which eight participants completed thousands of continuous recognition trials while undergoing fMRI. Participants judged whether each image had been seen before to examine how mesolimbic activity varies with retrieval success under varying levels of contextual novelty. We classified trials to unpack both objective and subjective retrieval signals (i.e., hits, false alarms, correct rejections, misses), and computed the proportion of novel images within each run to quantify contextual novelty. We found that VTA activity was elevated when participants believed they had successfully recognized an image as familiar (hits and false alarms), whereas NAcc activity increased selectively for accurate recognition (hits only). Importantly, both regions showed increased recognition-related activity for hits in runs with higher contextual novelty. These findings suggest that mesolimbic responses during memory retrieval reflect the reward value of memory success over novelty but are modulated by contextual novelty. Future work will explore whether this pattern of results is driven by contextual novelty globally energizing the mesolimbic system, or if novelty increases the perceived salience of old events.

**Disclosures:** Y. Liu: None. I.C. Ballard: None. J.B. Hutchinson: None. V.P. Murty: None.

## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.08/TT7

**Topic:** I.10. Human Learning and Cognition

**Support:** Howard Hughes Medical Institute (HHMI)  
NIH (R35NS137370)  
Simons Foundation  
McGovern Institute

**Title:** Neural geometry of relational representation in the monkey posterior parietal cortex

**Authors:** \*S. PAENG<sup>1</sup>, S.-J. AN<sup>2</sup>, H. SOHN<sup>2,1</sup>, M. JAZAYERI<sup>3</sup>;

<sup>1</sup>IBS Ctr. for Neurosci. Imaging Research, Sungkyunkwan Univ., Suwon, Korea, Republic of;

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**Abstract:** Abstract relational reasoning is crucial for flexible cognition. A leading theory has proposed that such reasoning requires 1) explicit representations of abstract relations, and 2) appropriate binding of these relations to the sensory attributes (Doumas et al. 2008). We take this problem to the brain, asking how the neural population represents relational information and integrates it with sensory information. Specifically, we focused on area 7a of the posterior parietal cortex (PPC), which has been implicated in encoding spatial relations between object

parts (Chafee et al., 2007) and in performing reference frame transformation (Andersen et al., 1985). To probe the role of PPC in spatial relation reasoning, we trained monkeys on a relational memory task. On each trial, animals were presented with a cue (C) and a target (T) and had to memorize the spatial relationship between them (e.g., T to the right of C). Later, when presented with a new cue (e.g., C in the upper location), they had to use the remembered spatial relationship to infer the corresponding target location (e.g., upper-right) and make a saccade to that position. Animals learned the task successfully and were able to rapidly generalize to new relations and cue locations. We first tested whether spatial relations are encoded independently of absolute spatial locations. By analyzing large-scale recordings from 7a (using Neuropixels) while monkeys were performing the task, we found correlates of cue-target relations and cue locations in independent low-dimensional subspaces of the population activity. Notably, these subspaces preserved the two-dimensional spatial layout of both cue positions and cue-target relations. The spatial layout of the relational memory was reorganized in incorrect trials, suggesting behavioral relevance of these neural representations. Next, we asked how these separate representations are integrated to compute a saccade vector. Population geometry analysis showed that, during the delay period, the dominant signal encoded by the 7a neural population was the remembered spatial relation, while the integrated saccade target signal was present but weaker. Overall, these results suggest that 7a supports relational reasoning by encoding spatial relations and spatial locations in separable low-dimensional subspaces, and robustly maintaining the relation representations during the memory period to enable flexible, goal-directed actions.

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## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.09/TT8

**Topic:** I.10. Human Learning and Cognition

**Support:** NIH R01 MH129439  
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**Title:** Neural basis of approximate object counting in human single-neuron activity

**Authors:** \*S.-Y. AN<sup>1</sup>, E. MICKIEWICZ<sup>3</sup>, H. SOHN<sup>2</sup>, S. A. SHETH<sup>4</sup>, B. Y. HAYDEN<sup>5</sup>;  
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**Abstract:** The ability to estimate quantities and flexibly process numerical information is a core cognitive function that emerges early in development and is conserved across species. A prevailing theory posits that distinct neural systems support different number ranges: small quantities (typically 1-4) are processed rapidly and precisely, whereas larger quantities are estimated more slowly and with greater, number-dependent variability. Additionally, symbolic counting in humans likely relies on a separate system based on exact, sequential processing. However, how these systems interact to enable flexible numerical cognition remains unclear. To tackle this question, we designed a number-estimation task in which participants freely viewed visual stimuli containing 1-16 objects for two seconds and reported the estimated number. During task performance, we recorded single-neuron activity from multiple cortical areas—including the hippocampus, entorhinal cortex, anterior cingulate cortex, and orbitofrontal cortex—in neurosurgical patients (N=6). Participants exhibited significantly greater response errors when estimating large numbers of dots (12-16) than when estimating small numbers (1-4) ( $t(458) = 9.9007$ ,  $p < 0.001$ ). We found that approximately 20% of neurons exhibited number-selective tuning, with a notable bias: about 40% of these were tuned to small numbers (1-4). Preliminary analysis of population dynamics revealed that neural trajectories in state space diverged according to numerical magnitude, with greater separation for smaller numbers. This pattern may underlie the enhanced precision for small-number estimation and reflect the number-dependent scalar variability. Together, these findings shed light on how distinct representations contribute to different numerical ranges.

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## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

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**Topic:** I.10. Human Learning and Cognition

**Support:** This project was funded by the Italian Ministry of University and Research Program PRIN 2022 research initiative, CUP B53D23014270006

**Title:** P300 dynamics reflect hierarchical encoding and inferential reasoning in a transitive inference task

**Authors:** \*A. PAUL<sup>1</sup>, M. SEGRETI<sup>1</sup>, G. BARDELLA<sup>1</sup>, S. FAGIOLI<sup>2</sup>, S. FERRAINA<sup>1</sup>, E. BRUNAMONTI<sup>1</sup>;

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**Abstract:** Making appropriate decisions often relies on looking back to past experiences, connecting them through common elements. This is the case of serial order decision, as inferential reasoning allows individuals to deduce  $A > C$  if it is known that  $A > B$  and  $B > C$ , since item B links the elements A and C. The Transitive inference (TI) task is an experimental approach developed to investigate this type of decision making. TI requires participants to identify the hierarchical structure of a set of arbitrarily rank ordered symbols ( $A > B > C > D > E > F$ ) by learning (learning phase) the ordinal relationship between all the adjacent pairs ( $A > B$ ,  $B > C$ ,  $C > D$ ,  $D > E$ ,  $E > F$ ) and later, in a test phase, to compute the relationship between non-adjacent pairs as  $B > D$  or  $B > E$ . Analysing the decision performance by grouping items' pairs by their rank differences, it emerges that the choice accuracy gradually increases as the difference between items' rank differences in a pair increases. This symbolic distance effect (SDE) is used as an independent variable to experimentally modulate the difficulty of pair comparisons in the task. Previous studies highlighted that parietal and frontal brain areas are engaged during this decision process. However, how this modulation is reflected in the neural dynamics is poorly explored. Here we investigated how the degree of difficulty in this form of decision is reflected in EEG activity and how this modulation is shaped by the learning of the items' ordinal relation. We recorded EEG activity of 32 participants from 64 scalp electrodes during the learning and test phases of a six-item TI task. The analysis of the behavioural performance detected that the decision accuracy increased with the progression of the learning relations between adjacent items and that a significant SDE emerged in the test phase. These two behavioural modulations were significantly reflected in the corresponding mean amplitude of P300 over the Centro-parietal scalp regions in both phases of the task (Anova  $p < 0.05$ ). Additionally, the Centro-parietal P300 was significantly modulated by the rank's encoding of each item of the set. Collectively, these results complement previous findings on the neural basis of decision making by examining the time course of inference-based decisions during both the stimuli encoding and comparison with other stimuli.

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### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

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**Topic:** I.10. Human Learning and Cognition

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**Title:** Modeling transitive-inference-related decision making using the drift diffusion model reveals generalizable latent cognitive mechanism across human and non-human primates



**Authors:** \*M. SEGRETI, S. DAL SASSO, A. PAUL, F. DI BELLO, S. FERRAINA, E. BRUNAMONTI;

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**Abstract:** Decision-making often relies on mental models built by linking experienced facts or stimuli. This allows individuals to decide between options by evaluating information that is not directly accessible from perceptual evidence alone. This form of decision-making can be studied through transitive inference (TI) tasks, in which subjects learn the rank order of a set of abstract, arbitrarily defined symbols (e.g.,  $A > B > C > D > E > F$ ) and use this structure to infer the rank relation between any pair of items in the set - for example, choosing the higher between B and E. In performing this task, both humans and animals exhibit the symbolic distance (SD) effect: faster and more accurate decisions when the distance between the items' ranks is greater. This effect emerges because items with similar ranks have closer representations in the hierarchical structure of the set. The Drift Diffusion Model (DDM) is a computational approach developed to evaluate the variables underlying decision-making processes. By conceptualizing decision-making as a ramping-to-threshold process, the DDM can determine whether decision difficulty depends on the accumulation rate ( $\nu$ ) or on the amount of evidence required to reach a decision, defined as decision boundary ( $\alpha$ ). Previous studies on perceptual decision-making have highlighted variation in  $\nu$  as the main factor accounting for different levels of decision difficulty. In this study, we assessed if the DDM could reliably account for decision-making in the TI task and which variables best explained decision difficulty in this task. Fitting the data from 83 humans and two rhesus macaques on a six-item TI task, the DDM reproduced both accuracy and reaction times with a high goodness of fit. However, the analysis of the model parameters revealed that  $\nu$  was the main factor accounting for task difficulty in humans. In monkeys, task performance was influenced by both  $\nu$  and a time-dependent collapse of  $\alpha$ , reflecting increased urgency in the monkeys' responses and a reduced level of decision caution as time progressed. To further explore the mechanism underlying the decision processes, we used the DDM to model the monkeys' performance after the injection of a sub-anesthetic dose of ketamine, an NMDA-receptor antagonist that we hypothesized would interfere with the ramping process, as it has been shown to impair rule-based decisions. After pharmacological treatment, we observed a reduced  $\nu$  along with a more pronounced collapse of  $\alpha$ , indicating more impulsive responses. These results highlight that the DDM can be consistently applied across diverse decision-making processes to estimate the latent variables underlying cognitive decision mechanisms.

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### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.12/TT11

**Topic:** I.10. Human Learning and Cognition

**Support:** Max Planck Society  
Max Planck School of Cognition

**Title:** Investigating the role of neural replay in multi-agent navigation

**Authors:** \*M. HINRICHS<sup>1</sup>, N. MENGHI<sup>1</sup>, Y. XU<sup>1</sup>, N. W. SCHUCK<sup>2,3</sup>, C. F. DOELLER<sup>1,4</sup>;  
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**Abstract:** In rodents, the fast sequential reactivation (i.e., replay) of hippocampal place cell sequences has been suggested to be involved in spatial memory consolidation and path planning. However, navigation rarely happens in isolation and often includes knowledge about anticipated or past movement of others, for instance, to avoid collision in physical space. While previous studies investigated individual spatial cognition, we know little about coordinated multi-agent navigation and whether replay plays any role in it, by prospectively simulating future trajectories of others and retrospectively replaying their past trajectories. Here, using recent methodological advances that can track replay in fMRI, we investigated pairs of participants who navigated a previously learned abstract state space in an interactive setting, trying to reach a common goal state while avoiding collisions, while their brain activity was measured using fMRI hyperscanning using two Siemens 3T MR scanners in parallel. The state space contained a bottleneck that both participants had to pass, ensuring that successful task performance required participants to consider both their own and the other's states. Behavioral results ( $N = 44$ ,  $M_{\text{age}} = 27.02$ ,  $SD_{\text{age}} = 4.56$ , female = 27) showed that participants improved their performance over trials, using their knowledge of the state space to navigate in the interactive setting successfully and reached the goal more often without colliding than expected by chance. fMRI data was analyzed using representational similarity analysis to show where the state space is represented in the brain. Furthermore, we identified replay-like events as the sequential reactivation of state representations by multivariate fMRI classification. Here, we looked at the prospective simulation of self and others' future trajectories during planning to avoid collisions, and the retrospective replay of their past ones for learning, indicative of a credit assignment mechanism. Our study sheds light on the role of replay in multi-agent navigation.

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**Poster**

**PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.13/TT12

**Topic:** I.10. Human Learning and Cognition

**Support:** Max Planck Society

**Title:** Mapping Brain Networks Underlying Sequential Mental Simulation

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**Abstract:** Our daily lives often involve navigating complex sequences of events that rely on diverse skills supported by distinct brain regions. For example, a student rehearsing her incoming day at school might mentally transition from recalling how to solve math problems to remembering Latin grammar rules to finally imagining running during a physical education class, consistent with the sequentially planned activities for the day. Each task might require the involvement of specialized brain regions, recruited in the correct temporal order. How does the brain coordinate such complex, sequential mental simulations? To address this question we trained participants to memorize three sequences of audio-visual-motor material, which would require distinct cortical modules to be activated in a specific succession. Participants rehearsed the sequences mentally using word cues and confirmed their memorization by identifying whether two stimuli were in the correct order or not. We used fMRI to record whole-brain activity during this task. Preliminary results showed that mental simulation was associated with reactivation of sensory-motor brain regions, including the occipital, superior temporal, and precentral cortices, corresponding to those identified via a separate localizer task for processing visual, auditory, and motor stimuli. Additionally, during the presentation of the cue we observed significant activation of the hippocampus and the medial parietal cortex, with the latter persisting for the entire simulation period. Planned further analyses, paired with a parallel study using MEG, will investigate 1) whether the parietal cortex and/or the hippocampus represent distinct sequences in their multivariate activity, 2) whether sequentiality is detectable in the temporal univariate activity profile of sensory-motor cortices, and 3) how these networks interact in terms of functional and causal connectivity.

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**PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

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**Program #/Poster #:** PSTR248.14/TT13

**Topic:** I.10. Human Learning and Cognition

**Support:** Max Planck Society

**Title:** Eye-movement patterns reveal efficient encoding and replay of multiple working memory items

**Authors:** \*Q. HUANG<sup>1</sup>, C. F. DOELLER<sup>1,2</sup>;

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<sup>2</sup>Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway

**Abstract:** Human cognition is constrained by limited attentional and memory resources, which restrict how much information we can process and retain. Efficient coding theory suggests that these limitations shape representational codes optimized for the environmental statistical regularities. Eye movements play a crucial role in actively exploring both the external world and internal mental representations, reflecting memory content, spatial relations, and conceptual structures. Here, we investigate whether eye movements facilitate the optimal mental organization of information to enhance working memory efficiency. To address this question, participants were presented with three gratings simultaneously, each differing in color (spanning green to blue) and spatial frequency, and were instructed to remember all stimulus features. Critically, gratings with lower frequencies were consistently paired with greener hues in the color spectrum. We found that trials sharing the same spatial configuration elicited more similar eye-movement trajectories both during encoding and maintenance, compared to trials with different configurations, an effect that correlated with behavioral performance. Furthermore, during encoding, high-performing participants exhibited clearer sequential eye movements, sampling from the lowest to the highest frequency grating—suggesting an efficient mental path for information organization. Intriguingly, under increased task difficulty, sequential replay of these gaze patterns emerged during the maintenance phase. These findings demonstrate that eye movements reveal the efficient mental organization of multiple memoranda and underscore their functional role in actively maintaining information in working memory.

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## **Poster**

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

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**Program #/Poster #:** PSTR248.15/TT14

**Topic:** I.10. Human Learning and Cognition

**Support:** ERC Starting Grant N. 804422

**Title:** Foraging in conceptual spaces: hippocampal oscillatory mechanisms behind semantic search

**Authors:** \*G. GIARI<sup>1</sup>, S. VIGANÒ<sup>2,1</sup>, R. MAI<sup>3</sup>, C. F. DOELLER<sup>4</sup>, R. BOTTINI<sup>1</sup>;

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**Abstract:** Neuronal recordings and cognitive neuroimaging have highlighted the hippocampal formation as a key region for representing relational knowledge of both spatial information and abstract concepts in memory. However, how do we search and access stored knowledge? During navigation, the hippocampal formation displays rhythmic oscillatory activity, particularly in the theta and gamma band. More specifically, the theta rhythm plays a crucial role in spatial memory: for instance, it conveys information about traveled distance and velocity. Gamma band is instead often coupled to the theta rhythm through phase-amplitude coupling. Here we asked whether these physiological signatures of hippocampal engagement during physical exploration also extends to mental exploration of abstract spaces, such as when recalling concepts from memory.

To answer this question we used stereo-EEG to record local field potentials from the hippocampus of 20 epileptic patients while they performed simple categorical verbal fluency tasks, randomly “foraging” for concepts from different categories (animals, professions, or cities).

Replicating previous results, searching for concepts in semantic memory gave rise to behavioral patterns balancing exploration and exploitation typical of animal foraging. As it happens in physical space, semantic distance between subsequent concepts tended to be minimized, with searching behavior proceeding in clusters of semantically related words, with occasional jumps to new clusters. In terms of neural activity, we observed that prior to word production—when participants were searching for and retrieving a concept from memory—the oscillatory component of hippocampal theta power significantly increased, mirroring similar effects observed during spatial navigation in both rodents and humans. Moreover, theta power was significantly modulated by semantic distances, increasing proportionally to the difference, in meaning, between subsequent words. Furthermore, phase-amplitude coupling between theta and gamma increased when participants switched between clusters of semantically related words. These results suggest that physiological signatures of hippocampal activity during physical exploration might also extend to mental exploration of abstract spaces, and potentially reveal novel mechanisms underlying the access of conceptual information from memory.

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**Topic:** I.10. Human Learning and Cognition

**Support:** ERC Starting Grant (NOAM - grant agreement No 804422)

**Title:** Visual experience influences entorhinal grid orientation stability

**Authors:** \*F. SIGISMONDI<sup>1</sup>, K. JASMIN<sup>2</sup>, V. RUBINO<sup>1</sup>, R. BOTTINI<sup>1</sup>;

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**Abstract:** Cognitive maps support humans' ability to navigate across spatial and relational knowledge. Their activity is supported by a neuronal population known as grid cells, located in the Entorhinal Cortex (EC). In humans, a proxy of grid-cell activity in the EC, grid-like coding, can be observed as a 60° modulation of the BOLD signal (6-fold symmetry). Recently, it has been reported that lack of visual experience influences the emergence of the standard neural geometry of EC cognitive maps during a spatial navigation task. However, whether this alteration persists also when navigating non-spatial relational knowledge, remains unclear. Thirty-four Early Blind (EB) and thirty-four Sighted Controls (SC) were asked to navigate a sound space defined by pitch and duration. In two fMRI sessions held on separate days, participants performed a sound-analogy task, judging whether changes in pitch and duration were identical (or not) across sound pairs. Data were analysed using the quadrature filter technique to examine the presence of 6-fold symmetry in the EC. Within-days analysis (where we estimated and tested the orientation of the grid within each day, cross-validated) detected a significant positive 6-fold symmetry in the EC of both groups, with no difference across them. However, when examining the consistency of grid orientations across the two days, we found that EB individuals consistently shift their main grid orientation by 30° from one day to the next, whereas in sighted people the grid orientation remained the same across days, as previously observed in similar experiments. This inconsistency of grid orientations across days resulted in the detection of a negative 6-fold symmetry in the EB group when we performed the quadrature filter analysis across days (i.e., grid orientation estimated on one day and tested on the other). Our results suggest that both SC and EB individuals rely on EC cognitive maps to navigate and organize relational knowledge. However, the lack of visual experience influences the stability of the entorhinal grid orientation. Further analysis will investigate whether such orientation shift leads to detectable behavioral effects

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**Title:** Movement in conceptual spaces is represented in gaze patterns and the entorhinal cortex

**Authors:** \*A. EPERON<sup>1</sup>, C. F. DOELLER<sup>2</sup>, S. THEVES<sup>3</sup>, R. BOTTINI<sup>4</sup>;

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**Abstract:** There is growing evidence that spatial memory mechanisms in the entorhinal cortex are used to navigate conceptual spaces. Nonetheless, it is unclear how these translate to non-spatial domains. Specifically, there is no clear analogue for self-motion-derived velocity input, sometimes referred to as ‘action’ in grid cell models, in non-spatial scenarios. In this study, we tested if the entorhinal cortex represents action in a conceptual space, and explored the underlying mechanisms using eyetracking. To do so, participants were taught to transition between numerically-labelled states using different mathematical operations (actions), and then measured eye movements and neural responses (using fMRI) while participants viewed individual numbers. We found that neural pattern similarity in the right entorhinal cortex scaled with the similarity of action possibilities across the states. Moreover, eye movement direction reflected the numerical sign of possible operations and was strongly connected to task performance. Finally, the eye movement effect correlated with the multivariate action-based effect in the entorhinal cortex at a group level. This could be taken as an indication that eye movements, or attention more generally, may reflect velocity input during the navigation of conceptual spaces.

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### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

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**Title:** Reactivation of prior memories during related learning results in differentiation of hippocampal representations in development

**Authors:** \*N. L. VARGA<sup>1</sup>, L. COHEN<sup>3</sup>, A. R. PRESTON<sup>2</sup>;  
<sup>2</sup>Neurosci., <sup>1</sup>The Univ. of Texas at Austin, Austin, TX; <sup>3</sup>Sch. of Educ., Univ. of California, Berkeley, Austin, TX

**Abstract:** The ability to link related events in memory is critical to knowledge extension, allowing individuals to combine information in new ways in support of inference. Past studies show children are less likely to infer links between events—a key determinant of knowledge acquisition and academic success. However, little is known about the neural mechanisms that limit memory linking through inference in development. Adult work shows that memories for related events are integrated in hippocampus to support novel inference. Such memory integration requires reactivation of related memories at the time of new learning, enabling linking of past and current events within the same neural ensemble. However, in development, hippocampal immaturity may limit memory integration even when past events are successfully reactivated. Instead, children may store related memories in different memory representations, limiting their ability to infer connections among those events. To test this prediction, children (7-12), adolescents (13-17), and adults (18-23) completed an associative inference task, wherein they learned initial associations (AB) followed by overlapping (BC) pairs during functional magnetic resonance imaging (fMRI) scanning. Before and after learning, participants viewed A and C images in isolation, enabling use of representational similarity analysis (RSA) to assess whether hippocampal representations for indirectly related events (AC) changed from pre- to post-learning, and how the magnitude of this representational change related to AC inference performance. Preliminary results show that inference improved with age ( $p=.01$ ) and that participants of all ages reactivated indirectly related items during overlapping learning, albeit less reliably so in adolescents. However, reactivation had different consequences for representation in development and adulthood (interaction;  $p=.01$ ). When children strongly reactivated prior memories, they showed greater dissimilarity—or differentiation—of related items in hippocampus ( $p = .02$ ) while hippocampal representation in adults trended toward integration and an intermediate pattern was observed in adolescents. Moreover, hippocampal integration was marginally associated with better inference at all ages ( $p = .08$ ). Therefore, our findings suggest that reduced inference performance in development may be due to limited hippocampal integration. Together, the findings underscore the consequences that learning-related neural computations have for reasoning and the need for future studies to identify interventions that may positively target them.

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**Topic:** I.10. Human Learning and Cognition



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NSF GRF 2023350133

**Title:** Neural representations of temporal regularities increase in scale and symmetry across development

**Authors:** \*O. FRIEND<sup>1,2</sup>, A. DUTCHER<sup>2</sup>, N. L. VARGA<sup>3</sup>, C. COUGHLIN<sup>5</sup>, A. R. PRESTON<sup>4</sup>;

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**Abstract:** To derive knowledge about the predictive structure of the world, it is necessary to learn statistical regularities about which events regularly occur together in time. In adults, sequences of events reliably occurring together are represented more similarly (i.e., integrated) in hippocampus and prefrontal cortex. Furthermore, adults represent event sequences symmetrically within hippocampus, such that memory for an early event evokes a later event and vice versa. These symmetrical temporal associations maximize temporal prediction about what events will follow each other in time. While hippocampus supports statistical learning of event sequences beginning in infancy, both hippocampus and prefrontal cortex undergo protracted maturation into young adulthood, suggesting that statistical regularities may be represented with increasing complexity during development. Here, we test the hypotheses that both the scale of temporal integration and the symmetry of sequence representation in hippocampus and prefrontal cortex will increase from childhood to adulthood. We used functional magnetic resonance imaging (fMRI) and a statistical learning paradigm to measure neural representations of temporal structure in children (ages 7-12, N=51) and adults (N=30). Participants viewed twelve novel 3D objects organized into four consistent triplets (ABC) across four fMRI runs. Objects were presented individually but always in the same triplet order, allowing participants to learn adjacent (AB) and non-adjacent (AC) relations as a metric of temporal integration scale. Six additional pre- and post-learning scans, during which participants viewed the objects in isolation without a predictable temporal structure to the presentation sequence, enabled quantification of representational similarity brought about by learning the temporal structure. First, we found that adults, but not children, show symmetrical representation of temporally adjacent sequence items in hippocampus (e.g., presenting A elicited reactivation of B and presenting B elicited reactivation of A). In contrast, children's hippocampal representations are asymmetric, encoding sequences in the forward direction only (e.g., A elicited reactivation of B, but B did not elicit reactivation of A). Moreover, adults, but not children, link non-adjacent (AC) events in medial prefrontal cortex, consistent with an increased scale of temporal integration with age. Collectively, these findings indicate both hippocampus and prefrontal cortex represent temporal regularities with greater complexity across development, forming more integrated representations of temporal structure with age.

**Disclosures:** O. Friend: None. A. Dutcher: None. N.L. Varga: None. C. Coughlin: None. A.R. Preston: None.

**Poster**

## **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.20/UU1

**Topic:** I.10. Human Learning and Cognition

**Support:** NIMH RO1 MH100121

**Title:** Hippocampus and medial prefrontal cortex interact to support acquisition of context-dependent hierarchical representations

**Authors:** \*O. ASHMAIG<sup>1,2</sup>, K. R. SHERRILL<sup>2</sup>, N. L. VARGA<sup>2</sup>, A. R. PRESTON<sup>2</sup>;  
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**Abstract:** Everyday decisions depend on the context in which they are made. For instance, knowing that apples (“object”) are found in grocery stores (“context”) and are sweet and healthy (“value”) allows us to predict where to find them and whether to consume them. In contrast, knowing that the same apples (“object”), when found lying on the ground (“context”), might be rotten or unsafe (“value”), may prevent us from consuming them. Prior work in rodents and non-human primates shows that after substantial training, hippocampus and medial prefrontal cortex (mPFC) maintain differentiated representations for an object (e.g., an apple) whose reward value varies by context. Here, we extend this work to test whether a similar representational scheme supports context-dependent decision making in the human brain, as well as quantifying how such representations emerge trial-by-trial during learning.

While undergoing functional MRI scanning, participants learned about objects with context-dependent reward values in a naturalistic, virtual environment consisting of an elongated, contextually-varying hallway with decision points on either end. Participants gradually learned that the reward value of three objects varied as a function of the context. For instance, the object that yielded the maximum points in one context was associated with the fewest points in the other context.

To quantify trial-by-trial learning processes, we fit two computational models to each participant’s choices, one isolating how prediction error changed dynamically during feedback and a second Bayesian state-space model that tracked accumulation of context-dependent knowledge. When these models were fit parametrically to neural data, we found that hippocampal and mPFC engagement and connectivity positively tracked prediction error during decision feedback, particularly early in learning. Moreover, we found that during the anticipatory hallway period prior to choice activation in both regions tracked the state-space parameter, indicating predictive reactivation of the knowledge space. Using multivariate pattern analyses, we also quantified how the individual object representations changed after learning. We found that participants with better behavioral performance showed enhanced differentiation of object-value representation by context in hippocampus and enhanced value differentiation in mPFC. These findings highlight how hierarchical representational structures and dynamic feedback-driven updating in hippocampus and mPFC jointly guide flexible, context-guided behavior.

**Disclosures:** O. Ashmaig: None. K.R. Sherrill: None. N.L. Varga: None. A.R. Preston: None.

**Poster**

**PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.21/UU2

**Topic:** I.10. Human Learning and Cognition

**Title:** Neural encoding of response accuracy in a realistic recognition memory task

**Authors:** \*A. LI, K. CHEAYE, H. HAFNER, L. JORDAN, C. MIKKELSEN;  
Program in Neurosci., Smith Col., Northampton, MA

**Abstract:** Previous research has demonstrated that hippocampal neurons are sensitive to the novelty vs. familiarity of visual stimuli (Jutras et al., 2010). However, there is little research on single-neuron responses to continuous visual stimuli in recognition memory in human subjects. In the dataset used for the present analysis, Keles et al. (2024) tested recognition memory using a movie-watching paradigm in human participants with epilepsy. Participants watched a clip from the movie “Bang, You’re Dead!”, and were shown images of scenes and asked to indicate whether they were novel or familiar, while single neurons were recorded in the medial prefrontal cortex, hippocampus and amygdala. We hypothesized that, 1) Performance of participants (correct vs. incorrect) can be classified based on neural firing rates, and 2) Classifier accuracy will be higher in high-performers vs. low-performers. To test these hypotheses, we first calculated firing rates for each trial. We then grouped participants into high vs. low performers using median split and created a classifier (using leave-one-out cross-validation) to determine if participant performance could be accurately classified from neural firing rates. Overall, our classifier did not classify participant performance significantly better than chance ( $t = 1.46$ ,  $p = 0.14$ ). However, classification accuracy was significantly higher for high-performing subjects vs. low-performing subjects, indicating that the classifier is better at classifying participant performance for high-performers compared to low-performers ( $t = 2.17$ ,  $p = 0.03$ ). These results indicate that neurons in recorded regions do not strongly modulate their firing rates by response correctness. Future analysis investigating associations between classifier accuracy and other psychological factors (such as participant confidence in responses, responses to specific visual stimuli, or neuropsychological measures) can shed light on the neural mechanisms underlying recognition memory. This research can ultimately help us understand how regions such as the hippocampus support healthy recognition memory, as well as how activity in these brain regions differs in patients with dementia or amnesia.

**Disclosures:** A. Li: None. K. Cheaye: None. H. Hafner: None. L. Jordan: None. C. Mikkelsen: None.

**Poster**

**PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.22/UU3

**Topic:** I.10. Human Learning and Cognition

**Support:** 2004344.1

**Title:** Contribution of Eye Movement Patterns to Representational Drift

**Authors:** \*Y. YUAN<sup>1</sup>, M. AOI<sup>2</sup>, J. SERENCES<sup>3</sup>;

<sup>1</sup>UCSD Dept. of Neurosciences, La Jolla, CA; <sup>2</sup>Neurobio. & Data Sci., UCSD, San Diego, CA;

<sup>3</sup>Psychology, UCSD, La Jolla, CA

**Abstract:** Representational drift, the phenomenon where neural activity patterns change in a systematic manner when exposed to the same stimulus, has been observed in mouse and human primary visual area (V1). However, given the complexity of movies and natural images, it's unknown whether the source of this change is intrinsic to neural computation or if animals and humans are covertly attending to a different set of features each time an image is presented. To investigate whether systematic changes in gaze or attention can contribute to representational drift, we ran a longitudinal eye-tracking study with complex visual stimuli repeated over time. 14 healthy adults (12F, 2M) participated in a free-viewing study over 6 sessions that spanned ~2 - 4 weeks. We tracked eye position while participants were presented with naturalistic images that repeated either within, across, or both within and across sessions. We regressed stationary gaze entropy against the number of times an image was repeatedly shown to the participants. Images with an empirical p-value < 0.05 were selected as proof of increasingly convergent or divergent attention allocation over time. We found that the time-scale at which this systematic spatial attentional shift onsets is highly individual-specific. Furthermore, we estimated the fixation density distribution for each image to highlight locations that were most commonly foveated across repeats to create an information density map. The information accumulation rate for each image was then quantified as the cumulative density from fixation to fixation. This cumulative function can be compared across sessions to investigate differing temporal characteristics of gaze on the same image repeated over time. While there were substantial differences across individuals, when averaged across participants, images presented in earlier sessions had a faster information accumulation rate than those presented in later sessions. This indicates that temporal gaze dynamics change systematically over sessions, suggesting yet another source of change that may contribute to representational drift. While speculative, these observations suggest that covert top-down cognitive factors such as shifts in attentional focus and eye position may bias neural encoding in a directional manner over time.

**Disclosures:** Y. Yuan: None. M. Aoi: None. J. Serences: None.

## Poster

### **PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.23/UU4

**Topic:** I.10. Human Learning and Cognition

**Title:** Multi-resolution clustering reveals variant and invariant brain states during longitudinal naturalistic viewing

**Authors:** \*Y. CHEN<sup>1</sup>, S. S. GHOSH<sup>2</sup>;  
<sup>2</sup>McGovern Inst. for Brain Res., <sup>1</sup>MIT, Cambridge, MA

**Abstract:** Introduction: What does the brain do when we watch TV shows? To follow who is doing what, where, how, and why, the brain transitions through dynamic states (e.g., spatiotemporal patterns of activity and coupling) that support perception, inference, and memory. But are these states shared across episodes, or shaped by episode-specific content? Using fMRI data from six seasons of Friends, we fit a sticky hierarchical Dirichlet process hidden Markov model (sHDP-HMM) to each episode and clustered the resulting states to identify invariant and context-dependent structure in large-scale brain dynamics.

Methods: We analyzed fMRI data from six participants who each viewed all six seasons of Friends (292 runs total, ~11 minutes each, TR = 1.49 s). Brain activity was parcellated using the Schaefer 400 cortical and Tian subcortex atlases. For each run, we fit an sHDP-HMM to infer latent brain states. We then clustered state patterns across episodes using hierarchical agglomerative clustering. To examine organization at multiple scales, we applied distance-based thresholds to the clustering dendrogram, focusing on coarse partitions (e.g., 2-3 clusters) and tracking how state structure evolved as the threshold increased.

Results: In a single participant, hierarchical clustering of sHDP-HMM-derived brain states yielded 2,127 fine-grained clusters at a high similarity threshold ( $r \geq 0.60$ ), gradually merging into three coarse clusters at the lowest threshold ( $r \geq 0.00$ ). This nested structure was robust across multiple resolution levels, with anti-correlated state pairs persisting until late-stage merges, reflecting strong functional antagonism. The broadest clusters captured opposing network configurations consistent with default mode and frontoparietal antagonism. Preliminary inspection across episodes indicated partial re-emergence of similar states, suggesting a blend of recurrent and episode-specific dynamics.

Conclusions: Hierarchical clustering of latent brain states identified a combination of consistent, large-scale patterns and episode-specific variations during extended naturalistic viewing. These results support the view that the brain reuses a core set of dynamic configurations while also adapting flexibly to narrative content. Analyses across participants and episodes further characterize the balance between context-invariant and context-dependent organization in large-scale brain dynamics.

**Disclosures:** Y. Chen: None. S.S. Ghosh: None.

**Poster**

**PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.24/UU5

**Topic:** I.02. Perception and Imagery

**Support:** ERC Adg (HUMANFACE 101055175)

**Title:** The neural basis of familiar face recognition with human intracerebral recordings

**Authors:** \*B. CERRAHOGLU<sup>1</sup>, C. JACQUES<sup>1</sup>, B. ROSSION<sup>2</sup>;

<sup>1</sup>Univ. of Lorraine, Nancy, France; <sup>2</sup>CRAN-UMR 7039, CNRS-Université De Lorraine, Nancy, France

**Abstract:** Accurate and rapid recognition of familiar faces is essential for social interactions, integrating visual processing with rich semantic and emotional associations. However, whether familiar faces engage distinct brain regions or modulate the same network as unfamiliar faces remains debated. Traditional hierarchical models propose that posterior ventral occipito-temporal cortex (VOTC) regions encode structural face features, while anterior temporal regions are engaged in accessing identity-related and person-specific information. Yet, evidence for this division has been inconsistent, partly due to methodological limitations. To address this question, we measured direct brain activity using electrodes implanted in the VOTC of a large group of epileptic patients (n=104) with extensive coverage. We employed a frequency-tagging paradigm optimized to measure familiar face recognition (FFR) - differential responses to familiar versus unfamiliar faces - using variable, naturalistic face images presented at upright and inverted orientations. Our findings reveal that FFR responses emerge early in posterior VOTC (detectable from around 130 ms post stimulus onset) and are broadly distributed, spanning posterior face-selective regions, including the inferior occipital gyrus and lateral fusiform gyrus, extending into anterior and medial temporal regions. These responses are strongly disrupted by inversion, indicating reliance on holistic face perception. Notably, in the upright condition, only 8% of familiarity-selective electrodes exhibited exclusive responses to familiar faces (i.e., no response to unfamiliar faces), indicating that although familiar and unfamiliar faces are processed differently, as evidenced by FFR selectivity, they rely on largely overlapping neural representations within the VOTC.

**Disclosures:** B. Cerrahoglu: None. C. Jacques: None. B. Rossion: None.

**Poster**

**PSTR248: Hippocampal and Cortical Representations of Memory, Space, and Abstract Structure**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR248.25/UU6

**Topic:** I.03. Decision Making

**Support:** NIH Intramural grant ZIA NS003144

**Title:** Hierarchical activity and coding in local modules of the human temporal lobe

**Authors:** \*J. I. CHAPETON<sup>1</sup>, K. SWIFT<sup>3</sup>, S. INATI<sup>2</sup>, K. A. ZAGHLOUL<sup>1</sup>;  
<sup>1</sup>SNB, <sup>2</sup>Neurophysiol. of Epilepsy Unit, NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, MD; <sup>3</sup>MIT, Cambridge, MA.

**Abstract:** The synaptic connectivity of local cortical circuits places constraints on neural activity, and these constraints have consequences on how information can be processed in the brain. Some of the difficulty tying structure to function in neural circuits lies in the fact that networks in the cortex exist not only at one spatial scale, but are thought to be organized at multiple scales ranging from mini columns to functional columns, and ultimately to whole brain networks comprised of interacting cortical regions. In a previous study we used recordings from micro-electrode arrays (MEAs) implanted in human participants undergoing seizure monitoring to show that at the scale of local circuits, the temporal lobe is organized into functional modules about 1mm in diameter, and these modules shape the underlying spatiotemporal patterns of neural activity. In our current work we are testing if this organization is consistent with the idea of hierarchical coding at different spatial scales.

Specifically, models of the functional role of modular organization in higher-order cortical regions posit that coding may be hierarchical in nature, such that specific spatio-temporal patterns of neuronal spiking are needed to distinguish two stimuli belonging to the same category, but information at the scale of cortical columns is sufficient for decoding the category of a stimuli. We directly tested this hypothesis by analyzing MEA recordings from human participants while they engage in a visual categorization task. During the task participants are asked to categorize images into 4 possible categories. Importantly, in a subset of blocks they are asked to distinguish between exemplars belonging to the same category; this allows us to test the prediction that the category of an image can be decoded from course-grained activity at the scale of cortical modules, whereas discriminations between exemplars of the same category require detailed knowledge of the activity of neurons within modules.

We find that (i) the category of the stimuli can be decoded at a rate significantly and substantially higher than chance by using course-grained (averaged) activity at the scale of cortical columns, (ii) decoding is better when course-graining based on module boundaries compared to averaging random groups, and (iii) individual exemplars from the same category cannot be decoded better than chance when using module level activity, but can be decoded by using the activity of the individual neurons. Together these results support the hypothesis of hierarchical coding at the scale of cortical modules in the human temporal lobe.

**Disclosures:** J.I. Chapeton: None. S. Inati: None. K.A. Zaghloul: None.

**Poster**

**PSTR249: Language Models and the Human Brain**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PST249.01/007

**Topic:** L11. Language

**Title:** Brains and language models converge on a shared conceptual space across different languages

**Authors:** \*Z. ZADA, S. A. NASTASE, U. HASSON;  
Princeton Univ., Princeton, NJ

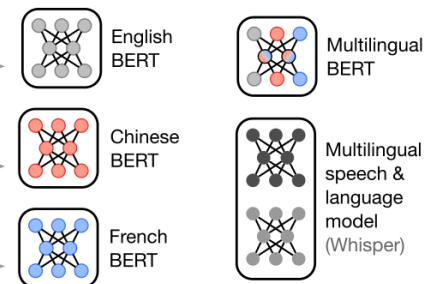
**Abstract:** Human languages vary widely in their forms, with different sounds, scripts, or syntax. Yet they all can convey the same meaning. Do different languages converge on a shared neural substrate for conceptual meaning? We used language models to identify neural representations of the shared conceptual meaning of the same story as heard by native speakers of three languages: English, Chinese, and French. We used an open fMRI dataset where three groups of participants listened to an audiobook of The Little Prince in their respective native languages: English, Chinese, and French. The story was ~100 minutes long and was divided into 9 scanning sessions. We aligned the audio and text across the three languages for each sentence, resulting in a total of 1650 sentences. Using the transcripts, we extracted word embeddings from three unilingual BERT models: trained solely on English, Chinese, or French. Despite the different models and languages, we found notable similarities between each pair of language embeddings after a simple rotation of the embedding features, especially in the middle layers. Next, we trained voxelwise encoding models to predict each subject's BOLD responses from the word embeddings for their native language. We found that BERT embeddings predicted activity throughout the language network for each language. Critically, we then evaluated how well the encoding model predictions generalize across languages. For example, we evaluated predictions from the English model trained on the brain activity of an English subject against the brain activity of French and Chinese subjects. We found that models trained to predict neural activity for one language in speakers of that language generalize to different subjects listening to the same content in a different language throughout high-level language and default-mode regions. Our results so far suggest that the neural representations of meaning behind different languages are shared across speakers of different languages and that language models trained on different languages converge on this shared meaning.



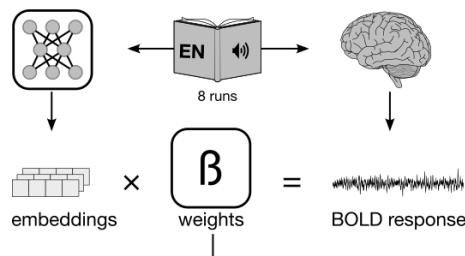
# A one narrative, three translations, three sets of participants



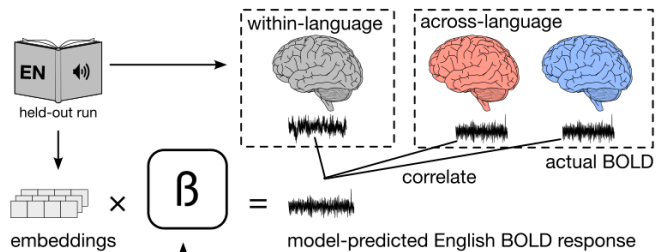
# B uni- and multi-lingual language models



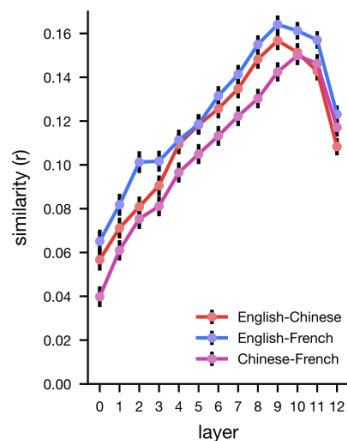
# C training voxelwise encoding models



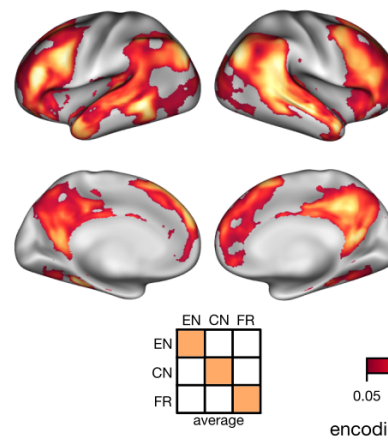
# D evaluating encoding models



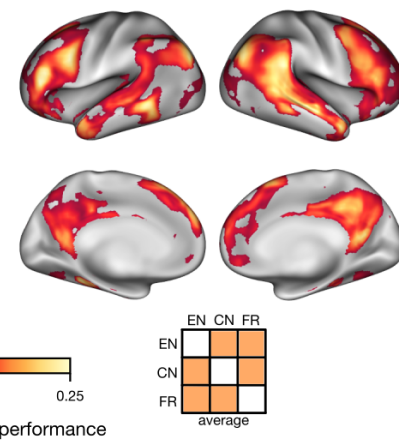
# E BERT embedding similarity



# F BERT within-language encoding



# G BERT across-language encoding



**Disclosures:** Z. Zada: None. S.A. Nastase: None. U. Hasson: None.

**Poster**

**PSTR249: Language Models and the Human Brain**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR249.02/UU8

**Topic:** I.11. Language

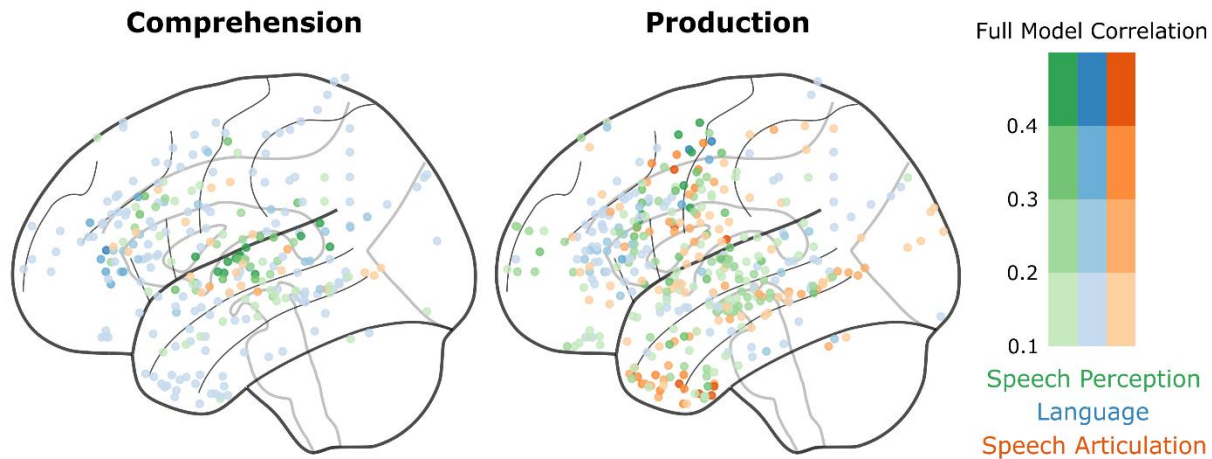
**Support:** NIH NINDS R01NS109367  
NIH NINDS R01NS115929  
DP1HD091948  
R01DC022534

**Title:** A Unified Speech-to-Text-to-Speech Brain Encoding Model for Natural Conversations

**Authors:** \*H. WANG<sup>1</sup>, A. GOLDSTEIN<sup>2,3</sup>, I. JALON<sup>1</sup>, Z. ZADA<sup>1</sup>, B. AUBREY<sup>1</sup>, L. NIEKERKEN<sup>1</sup>, W. K. DOYLE<sup>4</sup>, D. FRIEDMAN<sup>4</sup>, S. DEVORE<sup>4</sup>, O. DEVINSKY<sup>4</sup>, A. FLINKER<sup>4</sup>, S. A. NASTASE<sup>1</sup>, U. HASSON<sup>1</sup>;

<sup>1</sup>Dept. of Psychology and the Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; <sup>2</sup>Dept. of Cognitive and Brain Sci. and Business Sch., Hebrew Univ., Jerusalem, Israel; <sup>3</sup>Google Res., Mountain View, CA; <sup>4</sup>Sch. of Med., New York Univ., New York, NY

**Abstract:** Humans effortlessly alternate between speaking and listening during everyday conversations. Here, we investigated the neural basis of speech comprehension and production, leveraging 100 hours (half a million words) of spontaneous, naturalistic conversations and concurrent electrocorticography (ECoG) recordings. Recent advances in large language models (LLMs) allow us to capture and examine the contextual richness and diversity of real-world speech. We employed SeamlessM4T, a multimodal LLM supporting both speech and text input and output. We extracted (1) speech perception embeddings from the speech encoder, (2) language embeddings from the text decoder, and (3) speech articulation embeddings from the text-to-speech-unit decoder. We then constructed joint electrode-wise encoding models using banded ridge regression to predict neural responses. During comprehension, auditory areas like the superior temporal gyrus (STG) were best predicted by speech perception embeddings, while semantic regions like the inferior temporal gyrus (ITG) and angular gyrus were best predicted by language embeddings. During production, the precentral (preCG) and postcentral gyrus were best predicted by speech articulation and perception embeddings. Interestingly, the temporal pole showed strong encoding performance and was best predicted by speech articulation embeddings. Furthermore, our encoding model enabled us to track the temporal dynamics of speech comprehension and production. The full comprehension encoding model peaked in auditory regions (STG,  $M = 94$  ms,  $SD = 215$  ms) before semantic regions (ITG,  $M = 276$  ms,  $SD = 103$  ms,  $t(69) = -3.248$ ,  $p < 0.001$ ). Conversely, encoding for production exhibited a reverse temporal gradient, with ITG ( $M = -605$  ms,  $SD = 558$  ms) and preCG ( $M = -451$  ms,  $SD = 374$  ms) peaking earlier than other regions ( $p < 0.001$ ). Overall, our findings highlight the power of LLMs to capture the neural patterns unfolding in natural conversations: from sensory perception to comprehension, and from planning to motor execution.



**Disclosures:** H. Wang: None. A. Goldstein: None. I. Jalon: None. Z. Zada: None. B. Aubrey: None. L. Niekerken: None. W.K. Doyle: None. D. Friedman: None. S. Devore: None. O. Devinsky: None. A. Flinker: None. S.A. Nastase: None. U. Hasson: None.

## Poster

### PSTR249: Language Models and the Human Brain

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR249.03/UU9

**Topic:** I.11. Language

**Support:** NIH NINDS R01NS109367  
 NIH NINDS R01NS115929  
 DP1HD091948  
 R01DC022534

**Title:** Aligning neural activity for non-overlapping stimuli via a model-based embedding space

**Authors:** \*A. BHATTACHARJEE<sup>1</sup>, B. AUBREY<sup>1</sup>, W. K. DOYLE<sup>3</sup>, D. FRIEDMAN<sup>4</sup>, O. DEVINSKY<sup>4</sup>, A. FLINKER<sup>5</sup>, A. Y. GOLDSTEIN<sup>2</sup>, U. HASSON<sup>6</sup>, S. A. NASTASE<sup>1</sup>;

<sup>1</sup>Princeton Univ., Princeton, NJ; <sup>2</sup>Neurosci., Princeton Univ., Kohav Yair, Israel; <sup>3</sup>NYU, New York, NY; <sup>5</sup>Neurol., <sup>4</sup>New York Univ., New York, NY; <sup>6</sup>Princeton Univ., Professor, Princeton, NJ

**Abstract:** Recent studies in human neuroscience have positioned deep neural networks, such as large language models (LLMs), as holistic computational models for predicting neural activity in complex, real-world tasks, like natural language comprehension. To investigate this relationship, researchers typically fit subject-specific linear encoding models mapping LLM embeddings onto the particular neural variables in a given individual. A recent study has shown that estimating a data-driven shared response model (SRM) improves encoding performance and facilitates generalization across individuals. However, a key limitation of SRM is that it can only be

estimated for neural activity time-locked to a shared stimulus presented to all subjects. To overcome this limitation, we developed a novel “embedding SRM” algorithm that leverages encoding models. We first estimate encoding weights mapping the model features onto neural activity for each subject. These matrices share one axis (corresponding to the embedding dimensionality), are not stimulus-specific, and preserve the subject-specific functional tuning of individual neural variables. Next, we estimate transformation matrices, by minimizing SRM objective function, that align these encoding weight matrices across individuals. This enables us to extend SRM to non-overlapping stimuli and subject-specific behavior: the subject-specific transformation matrices estimated from different stimuli can be used to transform one subject’s neural activity to another subject’s neural activity space. We apply this method to two datasets, a naturalistic story-listening “Podcast” dataset (8 subjects, 5,037 words each) and a large dataset of speaking and listening in unique, individual-specific conversations (4 subjects, ~80,000 words each), and show that denoising individual data using embedding SRM significantly improves the LLM-based encoding model performance in held-out samples. Embedding SRM allows us to construct encoding models that generalize across subjects with performance comparable to within-subject encoding, for completely disjoint stimuli. This generalization method paves the way for more precisely modeling the new individuals and aligning neural activity that cannot be synchronized across individuals (e.g., spontaneous speech production).

**Disclosures:** A. Bhattacharjee: None. B. Aubrey: None. W.K. Doyle: None. D. Friedman: None. O. Devinsky: None. A. Flinker: None. A.Y. Goldstein: None. U. Hasson: None. S.A. Nastase: None.

## **Poster**

### **PSTR249: Language Models and the Human Brain**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR249.04/UU10

**Topic:** I.11. Language

**Support:** R01DC019653  
U01NS121616  
Mussallem Transformative Scholar Award

**Title:** A large language modeling approach reveals single neuronal elements of natural speech production in humans

**Authors:** \*J. CAI, Y. KFIR, M. JAMALI, S. S. CASH, Z. WILLIAMS;  
Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA

**Abstract:** Humans are able to effortlessly assemble words into meaningful sequences during natural speech. The basic cellular mechanisms that underlie sentence construction during natural speech, however, remain poorly understood. In this study, we obtained large-scale recordings from semi-chronically implanted microarrays as participants engaged in natural sentence

construction. Recordings were distributed in both temporal and frontal cortical areas across hemispheres shown to engage in language production and sentence-level processing. Next, to study the neurons' encoding dynamics, we utilized a Llama2-7b large language model (LLM) and obtained its hidden embeddings from all layers to represent the compositions of the sentences produced by the participants. By further comparing the artificial neuronal activity (LLM embeddings) to the recorded human neuronal activity, we found a detailed, hierarchical coding structure that supports language production. Specifically, we show that the LLMs reliably predict neural activity across all participants, suggesting that they are capable of tracking the dynamics of the progression of the words being articulated. We also show that neurons from anterior temporal cortices, posterior temporal cortices and frontal cortices encoded information about the composition of the sentences at different hierarchical levels, as the predictivity varies across these areas. Last, we find variations in the temporal dynamic of neuronal response across brain areas, with anterior temporal cortices showing consistent high predictivity shortly before word onset. Together, the integration of single-neuron recordings with LLM-based linguistic models reveals a fine-grained map of neuronal coding that could support the production of meaningful speech.

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## **Poster**

### **PSTR249: Language Models and the Human Brain**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR249.05/UU11

**Topic:** I.11. Language

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**Title:** Internal network dynamics in large language models and aphasic human brains

**Authors:** \*T. WATANABE;  
IRCN, Univ. of Tokyo, Tokyo, Japan

**Abstract:** Large language models (LLMs) can fluently generate seemingly persuasive answers to almost all questions. However, their responses are not always the case: they are often inaccurate and contain hallucinations. These behavioural characteristics resemble symptoms of receptive aphasia seen in humans with strokes. For example, individuals with Wernicke's

aphasia can speak with regular rhythm and grammatical accuracy, but their speech content frequently does not make sense. These behavioural similarities between LLMs and receptive aphasia in humans indicate similarities in internal information processing between them. Here, to examine this possibility, we compared the internal network dynamics between LLMs and human brains with a variety of aphasia. Technically, we used energy landscape analysis for this human-machine comparison. As a preparation, we analysed the collective neural dynamics underlying expressive and receptive aphasia and found that the degrees of polarisation of the transition frequency and dwelling time are the key for accurate classification of each brain dynamics pattern into expressive aphasia, receptive aphasia or controls. We then applied this result to the investigation of the internal network dynamics of LLMs—here, Google ALBERT, OpenAI GPT-2 and Meta Llama-3—and identified a similarity between internal dynamics in all the LLMs and collective brain dynamics seen in individuals with receptive aphasia. These results point out a possibility that we may be able to give a certain diagnosis to an LLM by comparing its internal network dynamics with typical/atypical human brain dynamics. This approach may also lead to developing a novel methodology to characterise LLMs, which would enable us to infer their performance even before using them and looking into their outputs.

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## **Poster**

### **PSTR249: Language Models and the Human Brain**

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**Topic:** I.11. Language

**Support:** Alchemist Brain to X (B2X) Project funded by the Ministry of Trade, Industry and Energy Grant 20012355; NTIS 1415181023

**Title:** Mapping neural correlates of word embedding geometry with representational similarity analysis

**Authors:** \*S. ROH<sup>1</sup>, C. CHUNG<sup>2</sup>;

<sup>1</sup>Seoul Natl. Univ., Seoul, Korea, Republic of; <sup>2</sup>Neurosci. Res. Inst., Seoul Natl. Univesity, Seoul, Korea, Republic of

**Abstract:** Transformer-based language models enable precise vector representations of word meaning that align with brain activity during language comprehension (Goldstein et al., 2024; Mischler et al., 2024). However, isolated word production differs fundamentally from comprehension, as it involves active semantic retrieval and motor preparation without contextual cues. Whether transformer-derived semantic geometry is also reflected in neural activity under these conditions remains less explored. To address this, we apply representational similarity analysis (RSA) as a model-agnostic framework to test whether cortical activity mirrors transformer-derived semantic relationships with high temporal precision. Intracranial EEG was

recorded from 3 epilepsy patients performing a visual word reading task. Each trial lasted 4 seconds, beginning with a 1-second-fixation followed by word presentation. High-gamma amplitudes (70-170 Hz) were extracted and segmented into 250ms windows with 25ms overlap. Sentence Transformer embeddings for each of the 108 words in the stimulus set were clustered using hierarchical density-based clustering with grid search optimization, yielding 10 semantic clusters. 17 unclustered noise points excluded from further analysis. Semantic representational dissimilarity matrices (RDMs) were computed from cosine distances between full embedding vectors across cluster pairs. Neural RDMs were constructed for each electrode based on pairwise distances of time-resolved high-gamma activity for trials in each cluster. RSA was performed channel-wise using Spearman correlation between semantic and neural RDMs. Statistical significance was assessed via 3,000 permutations with false discovery rate correction. The neural activity recorded from each of the three participants reflected the semantic relationships between words, as captured by the word embedding model. Peak RSA values were  $r = 0.77$  in the left middle temporal gyrus, 0.69 in the right superior temporal gyrus, and 0.65 in the left anterior prefrontal cortex, at latencies from 0.25 to 1.35 s post-stimulus, spanning pre-speech through early and mid-articulation depending on stimulus word length. Mean RSA values ranged from 0.33 to 0.39 across individuals. These findings suggest that semantic clusters derived from transformer-based models align with fine-scale neural dynamics, supporting RSA as a powerful approach to probing distributed semantic representations in the human brain.

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## **Poster**

### **PSTR249: Language Models and the Human Brain**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR249.07/UU13

**Topic:** I.11. Language

**Title:** Characterization of LLMs with the Big Five factors of personality

**Authors:** \*K. INOUE<sup>1</sup>, Y. TAMORI<sup>2</sup>, S. YOSHIZAWA<sup>3,4</sup>, K. MOGI<sup>4,2</sup>;

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**Abstract:** Large Language Models (LLMs) such as ChatGPT are used in a wide range of fields emulating human cognition, including natural language processing, image generation, and programming, playing important roles in companionship, life organization, and therapy. As AI systems become increasingly integrated into human activities, there is a need for understanding the way LLMs handle and align with personality traits, described by e.g. the Big Five personality model (John et al,1991), which is based on psychometric parameters of openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism. Some studies have explored how LLMs can be constructed to exhibit Big five traits, with varied difficulties in reproducing

each trait (Hazuki et al,2024). Analyzing the linguistic behavior of LLM's from the BIG FIVE perspective would help better understand how humans could interact and align with LLMs, reflecting the variable personality traits of people. Previous research (e.g. Serapio-Garcia et al, 2023) used the correlations of Big Five traits to show convergent and discriminant validity in LLM personality measurements. Here we investigated how the BIG FIVE model could account for output characteristics of LLMs (Open AI ChatGPT and Google Gemini) under different constraints including the prompts, and in comparison with human assessments. We applied BFI (Big Five Inventory: John et al,1991), BFI-2 (Soto & John, 2017), and IPIP-NEO-test (International Personality Item Pool-NEO-test: Goldberg et al,1999) to LLM models, and examined how Big Five traits, including the independence of each factor, are perceived using correlation coefficients and compared the results with assessments of Big Five traits by human evaluators. We identified and characterized variabilities in the responses of the LLMs, as well as agreements and dissociations in BIG FIVE traits evaluations. We discuss cognitive constraints in the alignment of LLMs in terms of the variabilities of BIG FIVE traits.

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## **Poster**

### **PSTR249: Language Models and the Human Brain**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR249.08/UU14

**Topic:** I.11. Language

**Title:** Functional specificity in multimodal large language models and the human brain

**Authors:** \*C. WANG, J. LI;  
City Univ. of Hong Kong, Hong Kong, Hong Kong

**Abstract:** Recent large language models (LLMs) excel at complex linguistic tasks and share certain computational principles with human language processing. However, it remains unclear whether their internal components specialize in functions such as semantic versus syntactic processing, as observed in the human brain. To investigate this, we selectively disrupted components of a multimodal Chinese LLM to simulate aphasia—a disorder marked by specific language deficits following brain injury. We leveraged behavioral data from Chinese aphasic patients and healthy controls collected at the China Rehabilitation Research Center and Beijing Normal University (Bi et al., 2015; Han et al., 2013). The dataset includes 88 aphasic patients (29 females, mean age =  $45.7 \pm 13.2$  years) and 43 healthy controls (21 females, mean age =  $49.3 \pm 10.7$  years). We systematically lesioned individual layers, self-attention heads, and critical parameters within the LLM, then generated outputs on the “Cookie Theft” picture description task. To quantify how closely each lesioned model resembled aphasic speech, we compared its outputs against patient responses using BLEURT, COMET, and BERTScore—standard metrics in machine translation. To further validate that these lesions parallel specific aphasia subtypes, we evaluated each model on three behavioral tasks: word-associate matching, oral picture



naming, and oral word repetition. These tasks assess comprehension, production, and repetition—core diagnostic criteria for classic aphasia subtypes. Our results demonstrate that disrupting certain LLM components can reproduce behaviors characteristic of distinct aphasia profiles. Specifically, simulating semantic deficits akin to Wernicke’s aphasia was relatively straightforward, whereas reproducing the syntactic impairments typical of Broca’s aphasia proved more challenging. We hypothesize that because LLMs are trained on vast corpora of well-formed text and rely on autoregressive decoding, they retain strong syntactic regularities even when parameters are degraded, resisting the truncated, ungrammatical patterns seen in Broca’s aphasia. In summary, our findings reveal both parallels and divergences between the modularity emergent in LLMs and the human language system, offering new insights into how information is represented and processed in artificial and biological intelligence.

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## **Poster**

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**Topic:** I.11. Language

**Support:** National Science and Technology Innovation 2030 Major Program (2022ZD0204804)  
National Natural Science Foundation of China (32441106, T2421004, 31930053, 32171039)

**Title:** Frequency-based probing of syntax and semantics: comparative representational analysis between large language models and the human brain

**Authors:** \*J. AN, Q. WANG, F. FANG;  
Peking Univ., Beijing, China

**Abstract:** Large Language Models demonstrate strong abilities at both syntactic and semantic tasks, yet the extent to which their computations mirror human neural processes remains unclear. We propose a unified frequency-domain analysis framework to identify neuron-wise components in models and intracranial recordings that encode syntax and semantics. Using hierarchical frequency tags tied to word-, phrase-, and sentence-level structures, we probe diverse multilingual models spanning parameter scales, architectural revisions, and instruction tuning. Simultaneously, we analyze intracranial sEEG data from human participants performing tasks designed to isolate syntactic and semantic processing. We compute spectral power at each target frequency and identify significant neurons or electrodes using a unified pipeline, enabling a direct comparison between artificial and biological networks. We make three main contributions. First, we disentangle syntax and semantics in both model and brain representations by quantifying neuronal oscillations at target frequencies. Our results show that model-based

syntactic processing aligns more closely with human neural patterns than semantic processing does. Second, we investigate bilingual contexts—English versus Chinese—within the models and demonstrate that, despite identical semantic content, distinct neuron sets in both models and human cortex encode meaning in largely different ways across languages. Third, our frequency-domain framework applied across model sizes, architectural upgrades, and instruction tuning shows that increases in model scale or upgrades within a single model family do not necessarily improve semantic or syntactic alignment with human data; rather, alignment differences are larger between distinct model architectures. Our methodology establishes a principled pipeline to jointly probe syntax and semantics in artificial and biological networks. These results clarify how architectural revisions and instruction tuning drive alignment: syntactic correspondence with human brain data tends to improve more than semantic correspondence. Cross-language discrepancies further highlight the necessity of multilingual evaluation to assess biological plausibility. This work lays a foundation for future studies investigating whether model advancements follow human-like or distinct neural mechanisms.

**Disclosures:** J. An: None. Q. Wang: None. F. Fang: None.

## **Poster**

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**Topic:** I.11. Language

**Support:** National Science and Technology Innovation 2030 Major Program (2022ZD0204802)  
National Natural Science Foundation of China (T2421004, 31930053)

**Title:** Speech language models with brain-like phonology-to-semantics processing achieve superior language comprehension performance

**Authors:** \*S. ZHANG<sup>1,2,3,4,5</sup>, R. YANG<sup>2,3,4,5</sup>, G. CHEN<sup>2,3,4,5</sup>, F. FANG<sup>2,3,4,5</sup>, Q. WANG<sup>2,3,6</sup>;  
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**Abstract:** Humans comprehend speech by transforming acoustic input into phonological and, subsequently, semantic representations. Yet, the neural mechanisms underlying this hierarchy—particularly the phonology-to-semantics shift—remain poorly understood. While state-of-the-art speech language models (SLMs) excel at speech recognition tasks, whether brain-like temporal dynamics enhance their language comprehension remains unclear. Here, we integrated intracranial electroencephalography (iEEG) recordings with pretrained SLMs to assess hierarchical and temporal representational alignment during speech processing and their relation

to model performance. We recorded iEEG from 17 epilepsy patients as they listened to 52 Mandarin disyllabic words, organized into 26 phonological pairs sharing the same initial syllable and spanning two semantic categories. The same stimuli were presented to 11 pretrained SLMs to extract model activations. To characterize phonological and semantic encoding in the brain, we computed time-resolved representational dissimilarity matrices (RDMs) at each contact based on pairwise decoding accuracy. Model RDMs were constructed per layer, unit, and token window using pairwise cosine distances. Brain-model alignment was assessed via representational similarity analysis (RSA) to derive hierarchical and temporal alignment indices, which were then correlated with model performance. We provide empirical evidence that the human brain and SLMs share three core computational principles in processing speech. First, both contain units selectively encoding phonological, semantic, or shared representations. Second, the proportion of phonological units decreases, while that of semantic units increases along both brain and model hierarchies, suggesting a shift from phonological to semantic space. Third, shared units exhibit a temporal shift from phonological to semantic tuning, indicating their role as bridges in representational transformation. Notably, the temporal alignment index of shared units significantly predicted superior language comprehension performance. RSA further showed that phonological and semantic model representations aligned with primary auditory and higher-order language regions, respectively, mirroring the brain's hierarchical organization. Our findings reveal that brain-like temporal dynamics, rather than static organization, in transforming phonological into semantic representations directly enhance speech comprehension performance, highlighting how biological temporal processing principles can guide the development of more effective artificial language systems.

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Shanghai Rising-Star Program (24QA2705500)  
Shanghai Pujiang Program (22PJ1410500)

**Title:** Neural hierarchy for coding articulatory dynamics in speech imagery and production

**Authors:** \*Z. ZHAO<sup>1,2</sup>, Z. WANG<sup>3</sup>, Y. LIU<sup>1,4</sup>, Y. LI<sup>3</sup>, J. LU<sup>1</sup>, J. WU<sup>1</sup>;

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**Abstract:** Mental imagery is a hallmark of human cognition, yet the neural mechanisms underlying these internal states remain poorly understood. Speech imagery, the internal simulation of speech without overt articulation, has been proposed to partially share neural substrates with actual speech articulation. However, the precise feature encoding and spatiotemporal dynamics of this neural architecture remain controversial, constraining the understanding of mental states and the development of reliable speech imagery decoders. Here, we leveraged high-resolution electrocorticography recordings to investigate the shared and modality-specific cortical coding of articulatory kinematic trajectories (AKTs) during speech imagery and articulation. Applying a linear model, we identified robust neural dynamics in frontoparietal cortex that encoded AKTs across both modalities. Shared neural populations across the middle premotor cortex, subcentral gyrus, and postcentral-supramarginal junction exhibited consistent spatiotemporal stability during the integrative articulatory planning. In contrast, modality-specific populations for speech imagery and articulation were somatotopically interleaved along the primary sensorimotor cortex, revealing a hierarchical spatiotemporal organization distinct from shared encoding regions. We further developed a generalized neural network to decode multi-population neural dynamics. The model achieved high syllable prediction accuracy for speech imagery (79% median accuracy, nine subjects), closely matching the performance of speech articulation (81%). This model robustly extrapolated AKT decoding to untrained syllables within each modality while demonstrating cross-modal generalization across shared populations. These findings uncover a somato-cognitive hierarchy linking high-level supramodal planning with modality-specific neural manifestation, revolutionizing an imagery-based brain-computer interface that directly decodes thoughts for synthetic telepathy.

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## **Poster**

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**Program #/Poster #:** PSTR249.12/UU18

**Topic:** I.11. Language

**Support:** NINDS T32 NS061788  
NINDS KO1 DC019265

**Title:** Decoding and Characterizing the Intracranial Representation of Semantic Information

**Authors:** \*C. SMITH<sup>1</sup>, A. MAMELAK<sup>4</sup>, U. RUTISHAUSER<sup>5</sup>, N. BENTLEY<sup>2</sup>, M. J. NELSON<sup>3</sup>;

<sup>2</sup>Neurosurg., <sup>3</sup>Dept. of Neurosurg., <sup>1</sup>Univ. of Alabama at Birmingham, Birmingham, AL; <sup>5</sup>Dept. of Neurosurgery, AHSP #6432, <sup>4</sup>Cedars-Sinai Med. Ctr., Los Angeles, CA

**Abstract:** Current language-based brain machine interfaces (BMI) target the sensory-motor cortex to decode attempted speech, however, such systems would have relative difficulty distinguishing phonetically similar words like ‘fork’ and ‘fort’. Here we investigate the feasibility of incorporating semantic categories and characterize the neural semantic representations across cognitive tasks. We performed intracranial (sEEG and ECoG) recordings from 18 epilepsy patients while they performed a battery of 5 semantic processing tasks comprised of 3 language production tasks (picture naming, semantic category naming, and a category-fluency/noun-generation task) and 2 comprehension tasks (word-to-picture matching and semantic category matching). The comprehension tasks used both audio and text presentation of each word stimulus in different trials. The stimulus in each trial was a noun from one of 15 concrete semantic categories (tools, animals, foods, etc.). We trained linear support vector machines to classify the semantic category as well as the animacy of the item each trial within a single task based on the time-windowed high gamma power (70-150 Hz) from all channels recorded in each patient, with ample coverage of the left-hemisphere semantic language network in our dataset. Each task was analyzed using 20 instances of a decoder, the median performance across tasks for semantic category decodes ranges from 29.4% to 76.8% (chance = 6.7%) and for animacy decodes 85.4% to 96.5% (chance = 50%). We evaluated cross-task model generalization and found that models trained on a production task generalized best to other production tasks and generalized weakly, but still significantly, to comprehension tasks. Models trained on comprehension tasks generalized weakly, but still significantly, across all tasks, and did so to a comparable degree to production and comprehension tasks. Using on rank consistency analysis it was found that the left Inferior Frontal Gyrus contributes the strongest to semantic category decoding; the left Temporal Pole (TP), left hippocampus, and left posterior Middle Temporal Gyrus are also major contributors. The TP appears to contribute more to finer category decodes while the hippocampus may contribute more to superordinate (animacy) decodes. These results demonstrate the feasibility of decoding semantic information from the distributed semantic network in a way that can benefit language BMIs and reveal that some components of the neural code for semantic information are shared between production and comprehension, while some are task specific.

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## **Poster**

### **PSTR249: Language Models and the Human Brain**

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**Program #/Poster #:** PSTR249.13/UU19

**Topic:** I.11. Language

**Support:** Alchemist Project (20012355, Fully implantable closed loop Brain to X for voice communication) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea).

**Title:** Interregional Cortical Dynamics Underlying Semantic Decoding Before Speech

**Authors:** \*Y. PARK<sup>1</sup>, C. CHUNG<sup>2</sup>;

<sup>1</sup>Seoul Natl. Univ., Seoul, Korea, Republic of; <sup>2</sup>Neurosci. Res. Inst., Seoul Natl. University, Seoul, Korea, Republic of

**Abstract:** Despite major advances in brain-computer interfaces (BCIs), decoding high-level language representations prior to speech remains challenging due to the rapid and distributed nature of semantic processing. While prior efforts have primarily focused on acoustic or articulatory features, the spatiotemporal contributions to decoding semantic category information during the pre-speech period remain poorly understood. In this study, we investigated how semantic representations unfold in time by analyzing high-gamma (HG, 70-170 Hz) electrocorticography (ECoG) signals from twenty subjects performing a word-reading task involving body- and non-body-related words. HG activity was examined from word presentation to 500 ms, capturing the full pre-speech window across subjects.

Group-level time-resolved decoding was performed by pooling features across subjects within each Brodmann area (BA). This group-based analysis revealed significant classification accuracy above chance in both hemispheres ( $p < 0.05$ , FDR-corrected) identifying a temporally structured sequence of contributing BAs. In the left hemisphere, decoding followed a clear temporal cascade: early dorsolateral prefrontal cortex activation (50ms), progressing to the inferior temporal and fusiform gyri (350-400ms), and peaking in the supramarginal gyrus (500ms)—suggesting a frontal-temporal-parietal progression. In contrast, the right hemisphere showed a distinct sequence, beginning in visual and temporal pole regions (50-100 ms), followed by dorsolateral prefrontal cortex (200 ms), fusiform gyrus (400 ms), and angular gyrus (450 ms). Cross-temporal regression revealed predictive flow in the left hemisphere, notably from early dlPFC activity (0-150 ms) to later SMG responses (300-350 ms). The right hemisphere exhibited a strong but temporally circumscribed linkage from temporal pole (200-300 ms) to angular gyrus (200-300 ms; peak  $R^2 \approx 0.70$ ). These findings demonstrate that semantic category decoding is supported by temporally structured interregional dynamics during pre-speech, including a novel frontal-temporal-parietal cascade and a transient but highly predictive right-hemisphere interaction—laying the groundwork for BCIs that decode intended meaning before articulation, beyond traditional approaches focused on acoustic or motor output.

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**Poster**

**PSTR250: Biochemical and Molecular Techniques II**

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**Program #/Poster #:** PSTR250.01/UU20

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

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The Technology Innovation Program (No. RS-2024-00445152) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea)

**Title:** Multiplexer-based system development for multichannel neurochemical sensing

**Authors:** \*H. KWON<sup>1</sup>, S. HWANG<sup>2</sup>, Y. KWAK<sup>2</sup>, K. KIM<sup>1</sup>, J. LEE<sup>1</sup>, D. JANG<sup>2</sup>;  
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**Abstract:** Electrochemical techniques for neurotransmitter detection have been widely utilized to investigate synaptic signaling processes and pharmacological mechanisms in the central nervous system. With the growing demand for monitoring multiple animals or multiple brain regions simultaneously, multichannel measurement systems are becoming increasingly necessary. In this study, we developed a multichannel neurochemical sensing system based on multiplexers (MUXs). The system incorporates 16:1 and 2:1 MUX configurations and supports various electrochemical waveforms—including fast-scan cyclic voltammetry (FSCV) and multi-cycle square wave voltammetry (MCSWV). The system enables simultaneous measurement across up to 11 channels for FSCV (−0.4~1.3 V, 10 Hz) and 16 channels for MCSWV (0.1 Hz). Electrochemical systems are highly sensitive to displacement current and RC delays, unlike conventional electronic circuits, due to their reliance on oxidation and reduction current measurements. We conducted simulations to analyze the effects of parasitic resistance and capacitance in MUX components and derived appropriate selection criteria. The results showed that parasitic resistance had minimal impact on signal fidelity, while parasitic capacitance induced voltage delays and elevated current responses. Specifically, capacitance values exceeding 50 pF led to more than a 5% increase in measured FSCV current relative to a standard Transimpedance Amplifier(TIA)-only system, and capacitance over 100 pF caused more than a 5% increase in the rising time of the MCSWV applied voltage. Based on these findings, TMUX6119 (Texas Instruments, 6.4 pF) and ADG1206 (Analog Devices, 13 pF) were selected as final components for their low capacitance (<50 pF), minimizing distortion of fast-changing voltage waveforms and suppressing displacement current. The completed system was validated using dummy cells and in vitro dopamine sensing experiments. Current signals were independently and simultaneously acquired from all channels without observable crosstalk, and dopamine oxidation responses were resolved across channels. This system is expected to facilitate high-throughput electrochemical experiments in neuroscience, enabling simultaneous monitoring of multiple animal models while improving experimental efficiency and inter-subject comparability.

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## Poster

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**Program #/Poster #:** PSTR250.02/UU21

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** RS-2024-00339708

**Title:** Cross-acquisition of tonic dopamine and serotonin levels in vivo with interleaved scanning of MCSWV and N-MCSWV waveforms

**Authors:** \*K. KIM<sup>1</sup>, H. CHO<sup>1</sup>, S. HWANG<sup>2</sup>, Y. KWAK<sup>3</sup>, H. KWON<sup>4</sup>, J. JANG<sup>5</sup>, D. JANG<sup>6</sup>;  
<sup>1</sup>Hanyang Univ., Seoul, Korea, Republic of; <sup>2</sup>Biomed. engineering, Hanyang Univ., Seongdong-gu, Seoul, Korea, Republic of; <sup>3</sup>Biomed. Engin., Hanyang Univ., Seoul, Korea, Republic of; <sup>4</sup>Dept. of Electronic Engin., Hanyang Univ., Seoul-City, Korea, Republic of; <sup>5</sup>Electrical Engin., Hanyang Univ., Seoul, Korea, Republic of; <sup>6</sup>Biomed. Engin., Hanyang Univ., Seoul-City, Korea, Republic of

**Abstract:** Dopamine (DA) and serotonin (5-HT) are key neurotransmitters regulating various brain activities, such as behavior, emotions, and motivation through diverse neural circuits. Various studies have aimed to measure the changes in DA and 5-HT concentrations in the brain, by traditional methods like microdialysis and fast scan cyclic voltammetry (FSCV). However, these tools have limitations in analyzing neurotransmitter concentrations, including low temporal resolution and difficulty distinguishing between DA and 5-HT. Our group previously developed Multi-Cyclic Square Wave Voltammetry (MCSWV) to measure basal neurotransmitter concentrations with high spatial and temporal resolution, distinguishing them by their oxidation-reduction patterns. However, the oxidation signals of DA and 5-HT are still similar, making it challenging to differentiate each neurotransmitter's concentration. Therefore, an additional analytical method is needed to refine the data from MCSWV. In this work, we implemented a combined waveform technique with the N-Shaped Multiple Cyclic Square Wave Voltammetry (N-MCSWV), which selectively measures 5-HT, enabling effective separation and basal concentration measurement of DA and 5-HT. MCSWV and N-MCSWV are applied every 10 seconds periodically, ensuring the sensitivity and selectivity of each waveform for neurotransmitters. By the unique property of N-MCSWV, we could complement the information obtained from MCSWV for DA and 5-HT, ultimately allowing the extraction of only DA basal concentration. The developed waveform was validated for their ability to separately measure basal concentrations of DA and 5-HT mixture solution. Additionally, the waveform successfully differentiated and measured the basal concentration changes of DA and 5-HT in the nucleus accumbens of the rat brain. Future studies aim to investigate changes in neurotransmitter concentrations related to specific drugs and brain diseases such as depression.

**Disclosures:** K. Kim: None. H. Cho: None. S. Hwang: None. Y. Kwak: None. H. Kwon: None. J. Jang: None. D. Jang: None.



## Poster

### PSTR250: Biochemical and Molecular Techniques II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.03/UU22

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** RS-2024-00339708  
25212MFDS004  
The Technology Innovation Program (No. RS-2024-00445152) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea)

**Title:** Functionalization of carbon nanotube yarn (CNTY) electrodes via cyclic-voltammetric oxidation (CVO) significantly enhances surface capacitance and electrochemical performance

**Authors:** \*J. JANG<sup>1</sup>, H. CHO<sup>2</sup>, S. HWANG<sup>3</sup>, Y. KWAK<sup>2</sup>, H. KWON<sup>4</sup>, K. KIM<sup>5</sup>, J. LEE<sup>1</sup>, D. JANG<sup>6</sup>;

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**Abstract:** Carbon fiber microelectrodes (CFMEs) have long been the standard tool for in vivo electrochemical detection of neurotransmitters such as dopamine (DA) due to their small size and biocompatibility. However, CFMEs have inherent limitations, including electrode fouling, poor long-term electrochemical stability and asymmetric redox behavior that often results in a dominant oxidation peak and a diminished reduction peak. These characteristics reduce the accuracy of quantifying reversible electrochemical processes. In this study, we present carbon nanotube yarn (CNTY) electrodes as a high-performance alternative to CFMEs for dopamine sensing. CNTY electrodes possess a highly porous, three-dimensional structure with a large electroactive surface area, making them well-suited for surface modification and electrocatalytic enhancement. We employed cycle-voltammetric oxidation (CVO) to electrochemically activate the CNTY surface, introducing oxygen-containing functional groups and defect sites. This treatment significantly increased surface capacitance and enhanced faradaic charge transfer kinetics. We observed that increasing CVO treatment time led to a proportional increase in the background current peak around +0.2 V in FSCV, indicating an increase in redox-active functional groups. Compared to CFMEs, CVO-functionalized CNTY electrodes exhibited 15-20-fold higher current density per unit area, despite having a smaller geometric area. We confirmed a direct correlation between the increased background peaks around +0.2 V and the enhanced sensitivity of the CNTY electrodes to dopamine, underscoring the critical role of these surface functionalizations in overall electrode performance. Also, CNTY electrodes exhibited exceptional structural and electrochemical stability under repeated high-voltage stress, maintaining functional integrity at least 10 times longer than 7  $\mu$ m CFMEs under identical conditions. Furthermore, dopamine measurements using CNTY showed more symmetric

oxidation and reduction peaks, in contrast to the asymmetric redox profiles typically seen with CFMEs. This enhanced symmetry suggests improved electrochemical reversibility and electron transfer efficiency, contributing to more accurate detection of tonic and phasic dopamine dynamics. These results establish CVO-functionalized CNT yarn electrodes as a durable and sensitive tool that outperforms traditional carbon fiber electrodes in current density, redox fidelity, and long-term stability, supporting their potential use in chronic in vivo neurochemical monitoring.

**Disclosures:** J. Jang: None. H. Cho: None. S. Hwang: None. Y. Kwak: None. H. Kwon: None. K. Kim: None. J. Lee: None. D. Jang: None.

## **Poster**

### **PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.04/VV1

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** RS-2024-00339708

**Title:** Real-time quantification of tonic-level vancomycin for therapeutic drug monitoring

**Authors:** \*J. LEE<sup>1</sup>, H. KWON<sup>2</sup>, J. JANG<sup>3</sup>, Y. KWAK<sup>4</sup>, K. KIM<sup>1</sup>, Y. OH<sup>5</sup>, K. H. LEE<sup>5</sup>, D. JANG<sup>4</sup>;

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**Abstract:** Vancomycin is a glycopeptide antibiotic highly effective against Gram-positive bacteria, particularly multidrug-resistant strains such as Methicillin-resistant *Staphylococcus aureus* (MRSA). Due to its narrow therapeutic range and the risk of serious side effects including nephrotoxicity and ototoxicity, precise Therapeutic Drug Monitoring (TDM) is essential. Conventional clinical approaches, such as High-Performance Liquid Chromatography-Mass Spectrometry (HPLC-MS) and immunoassays, often require complex equipment, long processing times, and substantial manual labor. Here, we present a novel electrochemical method that enables real-time quantification of tonic-level vancomycin with remarkable simplicity and speed. By utilizing vancomycin's distinct second oxidation peak as a stable marker, we succeeded in estimating its concentration without compromising reliability. This work provides a compelling alternative to conventional TDM practices by enabling continuous and quantitative monitoring. We believe our approach can contribute to safer and more efficient vancomycin therapy, ultimately reducing the clinical burden on both patients and healthcare providers.

**Disclosures:** J. Lee: None. H. Kwon: None. J. Jang: None. Y. Kwak: None. K. Kim: None. Y. Oh: None. K.H. Lee: None. D. Jang: None.

## Poster

### PSTR250: Biochemical and Molecular Techniques II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.05/VV2

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT)(No. RS-2023-00266075)  
The Technology Innovation Program (No. RS-2024-00445152) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea)

**Title:** Comparative analysis of electric field distributions in temporal interference stimulation: constant current vs. constant voltage approaches

**Authors:** \*M. CHO<sup>1</sup>, M. MO<sup>2</sup>, S. SONG<sup>2</sup>, D. JANG<sup>2</sup>;  
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**Abstract:** Temporal Interference (TI) stimulation has recently gained notable attention as a noninvasive technique, particularly in applications such as deep brain stimulation (DBS) and peripheral nerve stimulation. It involves applying two high-frequency signals,  $f_1$  and  $f_2$  ( $f_2 = f_1 + \Delta f$ ), which overlap in space to produce an electric field oscillating at the average frequency  $(f_1 + f_2)/2$ . This field is modulated into an envelope at the beat frequency  $\Delta f$ , enabling effective low-frequency stimulation of neurons in deep targets. A notable advantage of TI stimulation is that the high-frequency components at the electrode placement site do not generate physiological effects. As a result, it permits concentrated deep stimulation while avoiding undesired surface-level activation. This distinguishes TI from traditional noninvasive methods by offering more precise targeting and reduced side effects. However, selective activation of deep targets may not always be ensured under all TI configurations. The distribution of the resulting electric field is influenced by the current delivery method, which could potentially lead to unintended surface stimulation. In this study, we quantitatively assess how constant voltage (CV) and constant current (CC) modes affect electric field distribution during TI stimulation. Using computational modeling, we analyze their effects on both the surface near electrodes and the intended deep target region. Electric field intensity is used as the key metric, as it plays a crucial role in triggering neuronal depolarization. In CV mode, the system dynamically adjusts current to maintain fixed voltage, responding to frequency-dependent impedance as defined by Ohm's law  $V = IR$ . Conversely, CC mode maintains a constant current by varying voltage, resulting in more spatially consistent and localized electric fields. The electric field is defined as  $E = J/\sigma$ , where  $E$  denotes the electric field strength,  $J$  is the current density, and  $\sigma$  is conductivity. These equations demonstrate how current source characteristics influence field distribution. The results suggest that CC stimulation is more effective in confining the envelope to deep regions by reducing cross-frequency interference and minimizing surface activation.

**Disclosures:** M. Cho: None. M. Mo: None. S. Song: None. D. Jang: None.

## Poster

### PSTR250: Biochemical and Molecular Techniques II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.06/VV3

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** the Ministry of Trade, Industry&Energy (MOTIE, Korea)/RS-2025-11442969

**Title:** Evaluation of lymphatic flow responses to increased respiratory volume induced via phrenic nerve stimulation in cynomolgus monkeys

**Authors:** \*Y. HUH<sup>1</sup>, M. CHO<sup>2</sup>, Y. LEE<sup>3</sup>, J. PARK<sup>3</sup>, C.-Y. JEON<sup>3</sup>, K. LIM<sup>4</sup>, D. JANG<sup>2</sup>;  
<sup>1</sup>Dept. of Electronic Engin., <sup>2</sup>Dept. of Biomed. Engin., Hanyang Univ., Seoul, Korea, Republic of; <sup>3</sup>Natl. Primate Res. Ctr., <sup>4</sup>Futuristic Animal Resource and Res. Ctr., Korea Res. Inst. of Biosci. and Biotech. (KRIBB), Cheongju, Korea, Republic of

**Abstract:** The lymphatic system maintains fluid balance, supports immune surveillance, and facilitates lymphatic clearance. Efficient lymph transport is essential for preventing lymphedema and neurological dysfunction. Recent studies suggest that respiration may modulate lymph flow by altering thoracic pressure and venous return. During inspiration, diaphragmatic contraction generates negative intrathoracic pressure, enhancing venous return and reinforcing lymphatic pressure gradients. Despite anatomical separation, lymph, blood, and CSF ultimately converge near the heart, indicating shared dependence on central circulatory dynamics. This study examined whether increasing respiratory volume via non-invasive phrenic nerve stimulation could enhance lymphatic flow. Cynomolgus monkeys (n=3) were anesthetized with isoflurane (1-3%) and stimulated at the supraclavicular region using bipolar electrodes. Electrical pulses (3-8 mA, 100  $\mu$ s, 25 Hz, 1.5 s) were triggered at the start of inspiration, increasing respiratory volume by ~50% (2.5  $\rightarrow$  3.75 slm). Respiratory flow and diaphragmatic motion were monitored using a flow sensor and ultrasound. To assess lymphatic flow, 0.5 mL of 1 mg/mL ICG was injected into the hand. Near-infrared (NIR) fluorescence videos were recorded at 25 fps for 10 minutes each during rest and stimulation. Videos were analyzed using MATLAB, including cropping, smoothing, and frame differencing to enhance dynamic signals. Coherent motion was then isolated using thresholding and morphological filtering. These were tracked across frames using centroid location, area, and intensity. Only consistent tracks were retained. For each trajectory, flow speed, area, and intensity were calculated. An integrated index combining these features represented lymphatic transport capacity. Stimulation significantly enhanced lymphatic transport. The average speed of tracked fluorescent flow events increased approximately 2-fold, with notable rises in area and intensity. The integrated flow index—combining velocity, extent, and intensity—increased by ~4.11-fold. All quantified metrics differed significantly between conditions ( $p < 0.01$ , Mann-Whitney U test). These findings demonstrate that phrenic nerve stimulation can enhance lymphatic circulation by amplifying respiration-driven mechanical forces. Quantitative increases in flow speed, signal area, and

intensity reflect improved transport efficiency. The results underscore the potential of respiratory modulation as a non-invasive strategy for enhancing lymphatic function, supporting further investigation in diverse physiological and clinical settings.

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## **Poster**

### **PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.07/VV4

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** The Technology Innovation Program (No. RS-2024-00445152) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea)

**Title:** Infra-slow respiratory rhythms drive sleep-dependent cerebrospinal fluid oscillations in humans

**Authors:** \*C. KIM<sup>1</sup>, J. LEE<sup>3</sup>, S. LIM<sup>4</sup>, P. H. MIN<sup>5</sup>, D. JANG<sup>2</sup>;

<sup>1</sup>Electronic engineering, <sup>2</sup>Biomed. Engin., Hanyang Univ., Seoul, Korea, Republic of; <sup>3</sup>Biomed. engineering, Hanyang university, Seoul, Korea, Republic of; <sup>4</sup>Radiology, <sup>5</sup>Neural Engin., Mayo Clin., Rochester, MN

**Abstract:** Sleep plays a critical role in memory consolidation, neural recovery, and metabolic waste clearance. This process is mediated by the glymphatic system, which becomes active during sleep and facilitates cerebrospinal fluid (CSF) inflow into the brain. CSF enters periaxonal spaces, exchanges with interstitial fluid (ISF), and removes neurotoxic solutes such as amyloid- $\beta$  and tau. Efficient CSF circulation during sleep is thus essential for glymphatic function. While arterial pulsation and slow neural activity have traditionally been considered primary drivers of CSF flow, recent studies suggest that respiration may serve as a distinct and powerful modulator. During inspiration, negative intrathoracic pressure enhances venous return and draws CSF toward the spinal canal; during expiration, this gradient reverses, promoting cranial CSF movement. However, whether such respiratory mechanics drive the large-amplitude, infra-slow CSF oscillations observed during sleep remains incompletely understood. This study investigates whether respiratory rhythms contribute to these oscillations. Multimodal physiological data—including functional magnetic resonance imaging (fMRI), electroencephalography (EEG), respiratory belt signals, and photoplethysmography (PPG)—were acquired from 33 healthy adults during natural sleep. CSF signals extracted from the foramen magnum revealed consistent oscillations at ~0.03 Hz. These CSF fluctuations were temporally aligned with increased respiratory volume (RV), decreased gray matter blood oxygenation level-dependent (GM BOLD) signal, reduced peripheral vascular volume (PVV), and broadband increases in EEG spectral power across delta to beta frequency bands. Cross-

correlation analysis of 2,719 CSF cycles demonstrated a temporally ordered sequence: RV peaked ~4 seconds prior to CSF inflow, followed by PVV reduction and EEG power elevation. This progression suggests that respiration initiates a cascade of physiological responses culminating in large-scale CSF oscillations. Additionally, phase-amplitude coupling analysis revealed that the infra-slow respiratory phase modulated the amplitude of CSF, RV, PVV, GM BOLD, and EEG signals in a phase-locked manner across modalities. These findings suggest that respiration functions as a supra-modal physiological synchronizer during sleep, coordinating neural, vascular, and CSF dynamics. By demonstrating that large-amplitude CSF oscillations are driven by respiratory rhythms, this study advances our understanding of glymphatic regulation and highlights respiration as a potential target for enhancing waste clearance and brain health.

**Disclosures:** C. Kim: None. J. Lee: None. S. Lim: None. P.H. Min: None. D. Jang: None.

## **Poster**

### **PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.09/Web Only

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** NIH/NIDA/IRP

**Title:** Sigma-1 receptor chaperone translocating within endoplasmic reticulum substructures when influenced by agonists or cellular stress

**Authors:** \*T. TRAN<sup>1</sup>, Y. YASUI<sup>2</sup>, T.-P. SU<sup>3</sup>;

<sup>2</sup>Cell. Pathobiology Section Integrative Neurosci. Br., <sup>1</sup>NIH, Baltimore, MD; <sup>3</sup>Cell. Pathobiology Section Integrative Neurosci. Br., NIDA-IRP, NIH, Cockeysville, MD

**Abstract:** Sigma 1 receptor (S1R) is a ligand-operated endoplasmic reticulum (ER) transmembrane protein concentrated in the ER-mitochondrion interface. S1R has drawn lots of attention recently because S1R agonists exhibit treatment effect against various neurodegenerative diseases including for example Alzheimer's disease in clinical settings. The ER contains two peripheral substructures: sheet and tubules, maintained respectively by ER proteins shaping either flatness or curvature. Interestingly, S1R has recently been shown to be a critical ER sheet-shaping protein. S1R is also known to translocate when stimulated by agonist or stress. Thus, it is important to understand the agonist or stress-induced dynamics of S1R translocation within the ER substructures. In this study, we treated Neuro2a cells with a S1R agonist, (+)-Pentazocine (10  $\mu$ M) or PRE084 (10  $\mu$ M), or a stress agent, thapsigargin (10  $\mu$ M) or H<sub>2</sub>O<sub>2</sub> (1 mM) for 30 min. Cells were labeled with antibodies against S1R, an ER sheet protein (LRRC59 or Climp63), or an ER tubule protein (RTN3 or RTN4). Confocal images were acquired, and Spearman's correlation coefficient was measured for co-localization of S1R with those protein markers. We found that stimulation with (+)-Pentazocine, but not PRE084, decreased the S1R co-localization with sheet protein LRRC59. However, both (+)-Pentazocine

and PRE084 did not alter Climp63. At the ER tubular, induced by (+)-Pentazocine, not PRE084, decreased S1R co-localization with RTN3 but no change was found with RTN4. Since (+)-Pentazocine changed the S1R co-localizes with ER sheet marker LRCC59 and ER tubules marker RTN3, we co-treated cells with S1R antagonist BD1063 (3 $\mu$ M) to examine if the (+)-Pentazocine effect is through S1R. The data showed that BD1063 could not block the effect of (+)-Pentazocine on the S1R co-localization with LRCC59 or RTN3, suggesting that (+)-Pentazocine effects were not through S1R. In stress tests, thapsigargin treatment did not alter the S1R co-localizations. However, H<sub>2</sub>O<sub>2</sub> treatment decreased the S1R co-localization with Climp63 and RTN3 but increased that with RTN4. Our findings show differential effects between (+)-Pentazocine and PRE084. The (+)-Pentazocine decreases S1R both in ER sheet and in ER tubules through unknown mechanisms without involving binding to S1R, whereas PRE084 has no effects. Further, the oxidative stress induced by H<sub>2</sub>O<sub>2</sub> appears to translocate S1R from ER sheet to ER tubule or within tubules, providing the first evidence that S1R can translocate within ER sheets and tubules under oxidative stress. Further research will extend our findings to the action of S1R neurobiologically as it pertains to different ER substructures.

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## **Poster**

### **PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.10/VV5

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Title:** Building structure activity relationships (SAR) to avoid unwanted CNS ion channel activity

**Authors:** \*R. A. ROBERTS<sup>1,2</sup>;

<sup>1</sup>Apconix, Macclesfield, United Kingdom; <sup>2</sup>Biosci., Univ. of Birmingham, Birmingham, United Kingdom

**Abstract:** CNS liability remains a significant cause of attrition throughout drug development both in pre-nonclinical and clinical studies. The involvement of numerous ion channels in CNS liabilities such as seizure provides an opportunity for a new paradigm in screening. Previously we have demonstrated the utility of iSLA, an in vitro liability assay based on 15 seizure-related ion channels (Nav1.1, Nav1.2, Nav1.6, Kv7.2/7.3, Kv7.3/7.5, Kv1.1, Kv4.2, KCa4.1, Kv2.1, Kv3.1, KCa1.1, Cav2.1, GABA- $\alpha_1\beta_2\gamma_2$ , nicotinic  $\alpha_4\beta_2$ , NMDA 1/2A). To assist in the development of therapies without liability, we embarked on a study to develop SAR (structure activity relationship) by identifying the specific structural characteristics of compounds associated with ion channel-related seizurogenic activity. Based on previous data, Nav1.2, Kv2.1 and GABA- $\alpha_1\beta_2\gamma_2$  were selected for this study. Compounds were selected from the Enamine REAL database with machine learning approaches using pharmacophore features and similarity to the selected test compounds from the original screen (amoxapine, diphenhydramine,

quetiapine, 4-AP, linopirdine, bepridil, NS1619, quinidine, verapamil, XE991). A total of 88 compounds (78 from the Enamine REAL database and 10 parent compounds) were screened by automated electrophysiology (QPatch II, Sophion) using CHO cell lines expressing human Nav1.2, Kv2.1 and GABA- $\alpha_1\beta_2\gamma_2$ . Six- (Kv2.1, Nav1.2) or 5-point (GABA- $\alpha_1\beta_2\gamma_2$ ) dose response curves were generated for each compound to generate IC<sub>50</sub> values. Initial screening using Kv2.1 and statistical analysis identified key pharmacophore pairs extracted may present a significant risk. This initial analysis provides evidence that some substructures may be more likely to inhibit Kv2.1, which may extend to other ion channels. Future work testing the compound set across more ion channels will provide more evidence and help to build a SAR predictive tool. This will help medicinal chemists avoid liability in the development of novel compounds.

**Disclosures:** **R.A. Roberts:** A. Employment/Salary (full or part-time): ApconIX.

## **Poster**

### **PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.11/VV6

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** David and Lucile Packard Foundation 2021-73005  
R01 MH125824  
P51 OD011132  
P51 OD011092

**Title:** Synthetic Serum Markers Enable Noninvasive Monitoring of Gene Expression in Primate Brains

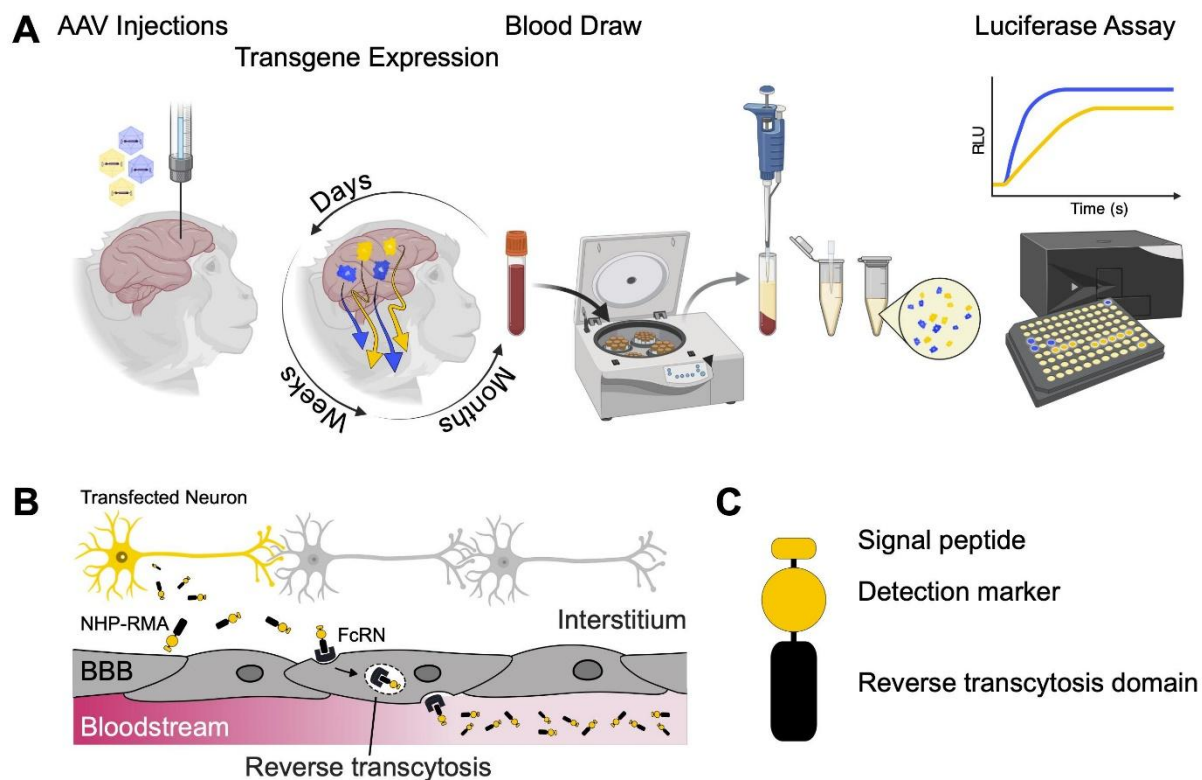
**Authors:** M. ROMAC<sup>1</sup>, S. LEE<sup>2</sup>, S. WATANABE<sup>3</sup>, M. M. CHERNOV<sup>4</sup>, H. LI<sup>3</sup>, E. RAISLEY<sup>3</sup>, J. O. SZABLOWSKI<sup>5</sup>, \*V. D. COSTA<sup>1</sup>;

<sup>1</sup>Emory Univ., Atlanta, GA; <sup>2</sup>Stanford Univ., Palo Alto, CA; <sup>3</sup>Rice Univ., Houston, TX; <sup>4</sup>Oregon Hlth. and Sci. Univ., Beaverton, OR; <sup>5</sup>Bioengineering, Rice Neuroengineering Initiative, Houston, TX

**Abstract:** Monitoring in vivo transgene expression is a barrier to deployment of molecular tools in nonhuman primates (NHPs). For example, monitoring of gene expression can be done through positron-emission tomography (PET) and/or magnetic resonance imaging (MRI), however, these neuroimaging techniques require specialized equipment, trained staff, bespoke contrast agents, and repeated anesthesia. Histological quantification of transgene expression is possible but requires biopsy or post-mortem analysis, which is often not feasible, ethical, or scientifically beneficial. We have developed a non-invasive and multiplexed method to repeatedly measure transgene expression in the NHP brain via a blood test using Released Markers of Activity (RMAs; Lee et. al., 2024). The macaque variant of RMAs (NHP-RMAs) consists of a signaling secretion sequence, a Gaussia (Gluc) or Cypridina (Cluc) luciferase reporter, and the Fc region of



the macaque IgG1 antibody. This allows the NHP-RMA to cross the blood-brain barrier via reverse-transcytosis and enter the blood, where the luciferase reporter concentrations can be measured and thus indirectly report transgene expression in the brain. We successfully injected AAVs, under the hSynpromoter, encoding either Cluc-based or Gluc-based RMAs ( $n = 5$ ; 1 male; ages 4.1-11.8; 6.4-11.85 kg) into cortical and subcortical brain regions. We demonstrate the ability to repeatedly monitor changes in AAV-mediated neuronal transgene expression using blood collection for up to 12 weeks. We also illustrate the NHP-RMAs are sensitive enough to monitor Cre-lox recombination in amygdalar-striatal circuits ( $n = 2$  females; ages 11.3-11.8; 7.3-9.1 kg). This technology can provide a non-invasive, repeatable, multiplexed, and cost-effective solution to assess gene expression in the brain in vivo in NHPs. This technology will make the use of molecular neuroscience tools more accessible in NHPs and more translatable in systems neuroscience.



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Poster

PSTR250: Biochemical and Molecular Techniques II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.12/VV7

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** RS-2025-00557203  
4199990113966

**Title:** A Lab-on-a-PCB Platform for Simultaneous Electrochemical Detection of Glucose, Lactate and Uric Acid

**Authors:** \*H. LEE, Y. HONG, H. SHIN;  
Kyungpook Natl. Univ., Daegu, Korea, Republic of

**Abstract:** Simultaneous measurement of multiple metabolic biomarkers is essential for the diagnosis and long-term management of chronic diseases such as diabetes, gout, and metabolic syndrome. However, conventional biochemical analysis systems rely on bulky and complex instruments, and often require labor-intensive sample preprocessing, making them unsuitable for point-of-care (POC) applications. To address these limitations, we present a miniaturized Lab-on-a-PCB platform capable of electrochemically detecting glucose, lactate, and uric acid in real time, with integrated signal processing and data transmission functionalities. The proposed system consists of two PDMS chambers, allowing for direct comparison between a control and a patient sample. Each chamber accommodates three gold working electrodes functionalized with glucose oxidase (GOx), lactate oxidase (LOx), and uricase (UOx), respectively, enabling parallel and quantitative analysis of the three target analytes. The Faradaic currents generated at each electrode are converted into voltage signals via transimpedance amplifiers (TIAs), and then digitized using an on-board 12-bit analog-to-digital converter (ADC). These signals are processed in real time by a microcontroller unit (MCU) embedded on the printed circuit board (PCB). The processed data is transmitted to a computer via a USB interface, where it can be visualized and stored using a custom Python-based graphical user interface. The system was validated in saliva and demonstrated high sensitivity, low detection limits, and minimal crosstalk between sensing channels. Furthermore, the modular architecture of the Lab-on-a-PCB platform allows for future expansion to additional biomarkers or integration with wireless power delivery systems. By incorporating sensing, signal processing, and data communication into a single board, this study presents a practical solution for next-generation multiplexed point-of-care diagnostic technologies.

**Disclosures:** H. Lee: None. Y. hong: None. H. Shin: None.

**Poster**

**PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.13/VV8

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** NIH Grant R01 NS129549  
NIH Grant R42 NS125895

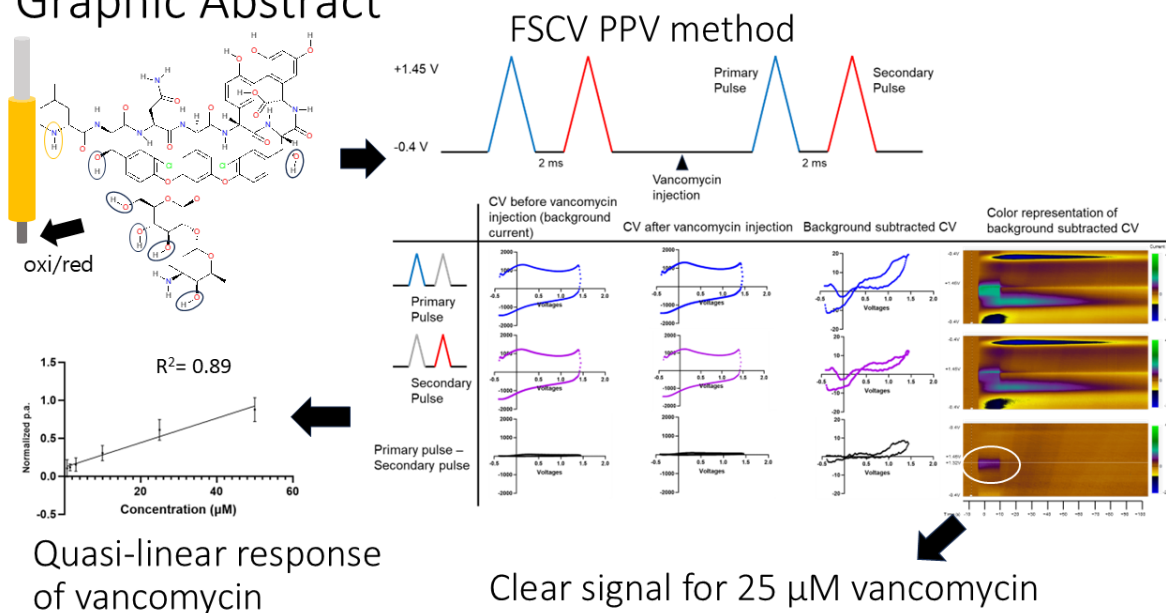
**Title:** Vancomycin Measurements Using Paired Pulse Voltammetry Applied by a Wireless Instantaneous Neurotransmitter Concentration Sensing (WINCS) System

**Authors:** \*S. TSAI<sup>1,5</sup>, M. HAWKES<sup>2</sup>, A. SAKUSIC<sup>3</sup>, S. HWANG<sup>6</sup>, Y. KWAK<sup>7</sup>, J. M. ROJAS CABRERA<sup>8</sup>, S. VETTLESON-TRUTZA<sup>3</sup>, K. SCHEITLER<sup>3</sup>, C. D. BLAHA<sup>3</sup>, J. CHANG<sup>9</sup>, D. JANG<sup>7</sup>, K. H. LEE<sup>3</sup>, Y. OH<sup>3</sup>, H. SHIN<sup>4</sup>;

<sup>1</sup>Neural Engin. and Precision Surgery Labs., <sup>2</sup>Neurol., <sup>4</sup>Neurologic Surgery, <sup>3</sup>Mayo Clin., Rochester, MN; <sup>5</sup>Neurol., China Med. Univ. Hosp., Taichung, Taiwan; <sup>6</sup>Biomed. engineering, Hanyang Univ., Seongdong-gu, Seoul, Korea, Republic of; <sup>7</sup>Biomed. Engin., Hanyang Univ., Seoul, Korea, Republic of; <sup>8</sup>Neural Engin. Lab. - Dept. of Neurologic Surgery, Mayo Clin. Alix Sch. of Med., Rochester, MN; <sup>9</sup>Yonsei Univ. Col. Med., Seoul, Korea, Republic of

**Abstract:** Vancomycin is an antibiotic used to treat serious bacterial infections, particularly those caused by Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). Often considered a last-resort treatment due to its potent antibacterial effects, vancomycin has a narrow therapeutic index that necessitates careful monitoring to prevent adverse effects like nephrotoxicity, ototoxicity, and blood dyscrasias. Current standards of care require continuous monitoring of serum concentrations in patients undergoing vancomycin therapy. However, the turnaround time for these results can take several hours, potentially delaying timely interventions for toxicity. Here, we propose fast-scan cyclic voltammetry (FSCV), an electrochemical technique that enables real-time monitoring of molecular concentrations by applying optimized potential waveforms and measuring the resulting oxidative and reductive currents, as an alternative method for monitoring vancomycin serum levels. We used the Wireless Instantaneous Neurotransmitter Concentration Sensing (WINCS) Harmoni system to apply FSCV. This device was previously developed by our lab and has a compact size, lightweight design, long battery life, and suitability for deployment in ICUs as well as other hospital and clinic settings as a point-of-care device. In this study, we investigated the feasibility of detecting vancomycin in vitro through waveform optimization, including the application of paired-pulse voltammetry. The method demonstrated a limit of detection of 0.36  $\mu$ M. We showed the potential of this approach for bedside, point-of-care use in critical care settings.

## Graphic Abstract



**Disclosures:** S. Tsai: None. M. Hawkes: None. A. Sakusic: None. S. Hwang: None. Y. Kwak: None. J.M. Rojas Cabrera: None. S. Vettleson-Trutza: None. K. Scheitler: None. C.D. Blaha: None. J. Chang: None. D. Jang: None. K.H. Lee: None. Y. Oh: None. H. Shin: None.

## Poster

### PSTR250: Biochemical and Molecular Techniques II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.14/VV9

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Title:** Development of Chimeric Monoclonal Antibodies to Facilitate Low-Plex Multi-Species Imaging of Key Brain Cell Markers

**Authors:** \*S. COVENEY, R. NIELSEN, G. INNOCENTI, N. PEDERSON, T. C. WIEDERHOLD, S. SINGH, R. W. CHO;  
Cell Signaling Technology, Inc., Danvers, MA

**Abstract:** There are several strategies for performing immuno-based multiplex imaging experiments. The most widely adopted method for multiplex imaging uses host-specific primaries where primary antibodies from various host-animals are indirectly detected by fluorophore-conjugated, host-specific secondaries. The most popular host animals include rabbit and mouse. Researchers often prefer monoclonal antibodies (mAb), rather than polyclonal, because they can exhibit superior and more consistent performance. However, neuroscientists often adopt host animals that include chicken, donkey, sheep, and guinea pig for primaries to

execute their host-based multiplex imaging experiments. Antibodies from these host animals are often polyclonal, exhibit poor specificity, and often have limited breadth of portfolio to key brain markers.

To address these issues, we developed chimeric antibodies (mouse/feline/horse) derived from highly specific rabbit mAbs targeting key neuronal, microglial, astrocyte, and oligodendrocyte markers using animal-free molecular biology techniques. Briefly, the Fc domain of the recombinant rabbit mAb was replaced with the Fc domain alternative species, Feline (IgG1), Horse (IgG4), and Mouse (IgG2a) Fc domains. We observed limited to no effect on chimeric antibody engagement to their target after Fc domain swapping. We also identified compatible secondaries that worked optimally in both brain tissue and cells, permitting researchers to adopt these chimeric antibodies into existing staining protocols and increasing host-antibody flexibility in their experiments.

To demonstrate the utility of the chimeric antibodies, we performed analysis of cell types surrounding amyloid plaques in an amyloid mouse model for Alzheimer's disease. Using chimeric antibodies, identified several microglia subtypes in the vicinity of amyloid plaques using a  $\beta$ -Amyloid Rabbit mAb and chimeric mAbs that recognize disease-associated microglia. Additionally, we combined our chimeric antibodies for neuronal markers as well as functional markers to assess neuronal activity, by detecting C-Fos activity in a subset of dopaminergic neurons in adult, wild-type mouse brain. In summary, CST's chimeric monoclonal antibodies increase flexibility to mix and match antibodies from various host-animals to enable multiplex experimentation.

**Disclosures:** **S. Coveney:** A. Employment/Salary (full or part-time): Cell Signaling Technology. **R. Nielsen:** A. Employment/Salary (full or part-time): Cell Signaling Technology. **G. Innocenti:** A. Employment/Salary (full or part-time): Cell Signaling Technology. **N. Pederson:** A. Employment/Salary (full or part-time): Cell Signaling Technology. **T.C. Wiederhold:** A. Employment/Salary (full or part-time): Cell Signaling Technology. **S. Singh:** A. Employment/Salary (full or part-time): Cell Signaling Technology. **R.W. Cho:** A. Employment/Salary (full or part-time): Cell Signaling Technology.

## **Poster**

### **PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.15/VV10

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** IHU FOReSIGHT [ANR-18-IAHU- 0001]  
NIH Grant U19NS104653  
NSERC Discovery Grant RGPIN-2021-03866  
Canadian Foundation for Innovation JELF 43065

**Title:** Chlok: a chemigenetic multicolor labeling system to visualize neuronal birthdate and circuit integration

**Authors:** \*G. FAINI<sup>1</sup>, M. TUFFERY<sup>1</sup>, A. SALEEM<sup>2</sup>, F. DU<sup>3</sup>, G. LE BOURDELLÈS<sup>1</sup>, K. DUROURE<sup>1</sup>, E. R. SCHREITER<sup>5</sup>, D. TANESE<sup>1</sup>, V. EMILIANI<sup>6</sup>, F. DEL BENE<sup>1</sup>, M. KOYAMA<sup>4</sup>;

<sup>1</sup>Vision Inst., Paris, France; <sup>2</sup>McGill Univ., Montreal, QC, ; <sup>4</sup>Biol. Sci., <sup>3</sup>Univ. of Toronto, Scarborough, Toronto, ON, Canada; <sup>5</sup>Janelia Res. Campus, HHMI, Ashburn, VA; <sup>6</sup>Photonics Dept., Vision Institut, Paris, France

**Abstract:** Understanding the developmental trajectory of individual neurons and the maturation of their functional roles within neural circuits is essential for elucidating brain development and plasticity during both embryonic and post-embryonic growth, when progressively more refined functions arise. Within developing circuits, newly generated neurons are gradually included into existing circuits by extending axons and dendrites and forming synaptic connections (1,2). Previous studies have been limited by low throughput and methodological limitations (3,4), highlighting the need for more advanced tools for examining neurogenesis and functional integration at the population level ideally in an *in vivo* preparation. To overcome these challenges, we present a birthdate-labeling strategy, based on HaloTag technology and a broad palette of synthetic JF dyes (6). We termed this approach **CHLOK** for **Chromatic HaloTag Labeling for cell Ontogeny tracKing**. The basic principle of this approach is to express HaloTag protein in differentiating neurons and then load a series of JF dyes with a temporally spaced schedule so that neurons differentiated in each interval get labeled with a distinct color. This methodology enables precise multicolor labeling of neurons according to their maturation stage. After validating CHLOK against the thymidine-based birthdating, we present a novel set of genetic constructs and labeling strategies. This includes age-dependent labeling of neuronal processes, simultaneous birthdating of up to five age groups, long-term tracking of age cohorts, and characterization of visual and motor responses in early and lateborn populations in the zebrafish larvae. Furthermore, we demonstrate the versatility of this approach, showcasing age-specific multicolor calcium and voltage imaging as well as optogenetic manipulation, demonstrating for the first time direct activity recording and manipulation of age cohorts. In conclusion, our novel birthdate labeling strategy CHLOK, provides a powerful, flexible, and non-invasive tool for studying *in vivo* neuronal integration and circuit development in the vertebrate brain, potentially extendable across multiple model organisms. CHLOK offers a significant advance over traditional methods by enabling single-cell resolution birthdate mapping, age-dependent functional imaging and all-optical control, opening new avenues for the study of brain development and plasticity. (1) Luo, L. (2021). *Science*. (2) Boulanger-Weill, J., et al. (2017). *Curr. Biol.* (3) Zhao, X., and van Praag, H. (2020). *Nat. Commun.* (4) Livet, J., et al. (2007). *Nature*. (5) Grimm, J.B., et al. (2017). *Nat. Methods*.

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**Poster**

**PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.16/VV11

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** Brain Canada Platform grant to ESR.  
Brain Canada to DF  
CIHR to DF  
Heart & Stroke fellowship to DF

**Title:** Non-viral transfection techniques for targeting radial astrocytes *in vivo*

**Authors:** \*O. RUGE<sup>1,2</sup>, D. FOUBERT<sup>3</sup>, E. RUTHAZER<sup>4</sup>;

<sup>1</sup>Neurosci., McGill Univ., Montreal, QC, Canada; <sup>2</sup>Neurosci. Grad. Program, Univ. of California San Francisco, San Francisco, CA; <sup>3</sup>Montreal Neurolog. Inst., McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada; <sup>4</sup>Montreal Neurolog. Inst., McGill Univ. Integrated Program In Neurosci., Montreal, QC, Canada

**Abstract:** Non-viral transfection is used extensively *in vitro*, whereas *in vivo*, viral methods are more common. As viral techniques are limited for insert size, large cell type-specific promoters are more amenable to non-viral methods. Viral methods may also induce inflammatory or immune responses in the transfected animal. We therefore compared three non-viral transfection techniques *in vivo*: electroporation, lipofection, and magnetofection. To target gene expression to radial astrocytes in the *Xenopus laevis* optic tectum, we injected circular plasmid DNA, complexed to cationic lipids, cationic lipids and ferrous nanoparticles or simply mixed with artificial cerebrospinal fluid into the brain ventricle of GCaMP6s-expressing tadpoles. For each technique, a genetically encoded fluorescent protein was transfected to measure transfection efficiency. The number of transfected cells, the distribution, and types of transfected cells were quantified to assess the efficacy of the techniques. Electroporation transfected many cells with a high specificity for radial astrocytes but also resulted in transient damage to the brain. Lipofection resulted in more transfected cells with lower expression levels. It was also found to elevate intracellular calcium levels. In contrast, we found that magnetofection was ineffective at sublethal doses in our model.

We then investigated the effects of these three techniques on cell proliferation and cell death. To quantify cell proliferation, we employed CldU (chlorinated thymidine analog) which is taken up by dividing cells and incorporated into DNA. For each technique, whole mount immunofluorescence labelling of fixed tadpole brains was performed using anti-BrdU and anti-tubulin antibodies (control). Increased proliferation may be an indication of more severe cellular damage. To address this, we also used propidium iodide (PI) to quantify cell death. Taken together, we found that lipofection offers the greatest efficiency with minimal negative side-effects.

**Disclosures:** O. Ruge: None. D. Foubert: None. E. Ruthazer: None.

**Poster**

**PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.17/VV12

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Title:** Optimisation of mRNA delivery to overcome transfection challenges in hiPSC-derived neurons

**Authors:** T. TATAR OZKAN, S. HUSSAIN, S. MILDE, F. MOSIS, **T. OOSTERVEEN**, \*A. BYRNE, W. BERNARD;  
bit.bio, Cambridge, United Kingdom

**Abstract:** Human induced pluripotent stem cell (hiPSC)-derived neurons represent powerful tools for advancing studies on human neurodevelopment and neurological disorders. Our range of neuronal subtypes, generated by opti-ox™ deterministic cell programming, offer a reliable source for functionality assays, drug screenings and disease modelling. However, the persistent challenge of efficient transgene expression upon DNA transfections in post-mitotic neurons may limit their use in a wide range of applications. As the nuclear envelope forms a barrier and limits the transcription of transfected DNA in non-dividing cells, we have used a mRNA-based transfection method that would only require cytoplasmic entry for translation. We developed an efficient and consistent, lipid-based messenger RNA (mRNA) delivery protocol specifically optimised for neurons, representing a significant technological advancement. Through systematic optimisation of critical parameters, including initial cell seeding density and the precise ratios of mRNA to lipofection reagent, our protocol achieved high transfection efficiency coupled with significantly reduced cellular toxicity and prolonged, sustained protein expression. Empirical validation with ioGlutamatergic Neurons, ioMotor Neurons, and ioSensory Neurons consistently demonstrated transfection efficiencies exceeding 90% with negligible cytotoxicity and robust long-term protein expression lasting up to 18 days. Moreover, being developed in 96-well plate format, our protocol significantly enhances robustness and scalability for high-throughput applications. Our experiments demonstrate that our opti-ox programmed neurons can be readily and effectively transfected with synthetic mRNA using our protocol, facilitating their utility in a broad range of molecular and functional assays. As a forthcoming application, we aim to apply this protocol for the overexpression of key neurodegenerative disease-associated proteins—such as TDP-43, alpha-synuclein, or MAPT—within our opti-ox programmed neurons, for a comprehensive assessment of its utility for studying disease-relevant phenotypes.

**Disclosures:** **T. Tatar Ozkan:** A. Employment/Salary (full or part-time): bit.bio. **S. Hussain:** A. Employment/Salary (full or part-time): bit.bio. **S. Milde:** A. Employment/Salary (full or part-time): bit.bio. **F. Mosis:** A. Employment/Salary (full or part-time): bit.bio. **T. Oosterveen:** A. Employment/Salary (full or part-time): bit.bio. **A. Byrne:** A. Employment/Salary (full or part-time): bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time): bit.bio.

**Poster**

**PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H



**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.18/VV13

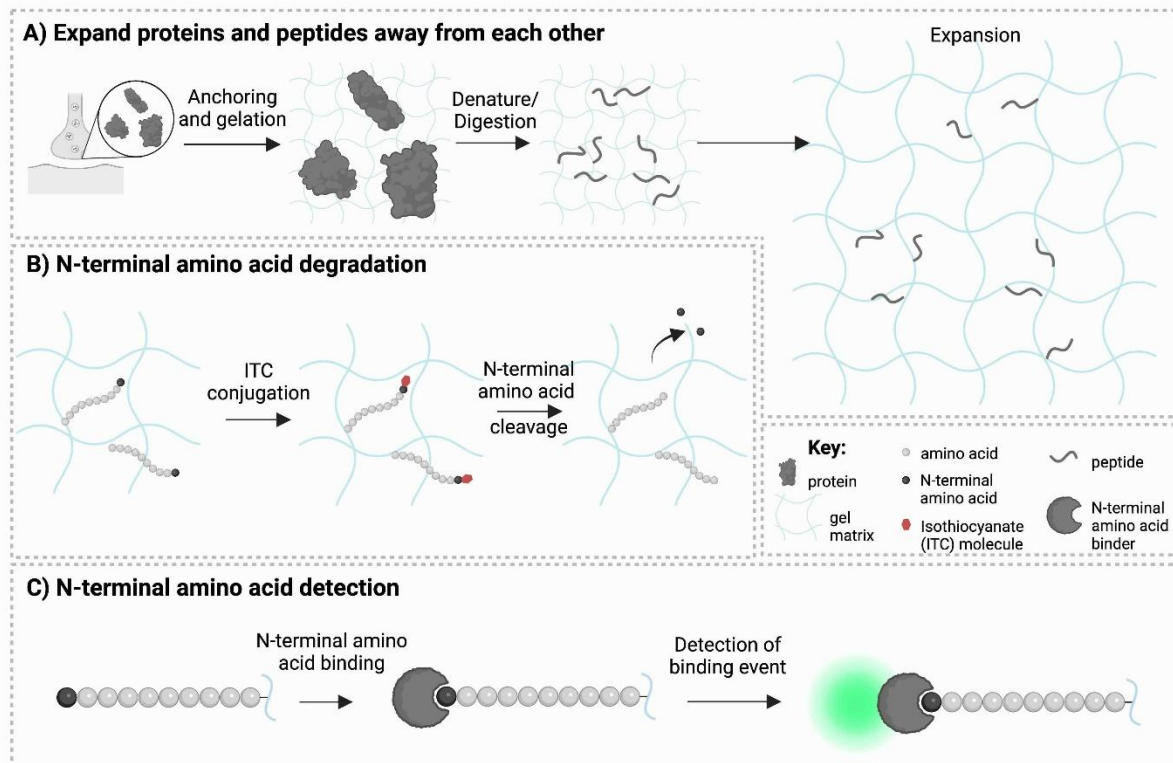
**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** Lisa Yang  
HHMI  
McGovern Institute  
Ashar Aziz  
NIH R01EB024261  
Jed McCaleb  
James Fickel

**Title:** Expansion Microscopy coupled to in-gel Edman degradation: a platform for in situ protein sequencing development and application

**Authors:** \*C. M. MITCHELL<sup>1,5</sup>, S. ZOGHI TAVANA<sup>2</sup>, J. PENG<sup>2</sup>, J. SHI<sup>2</sup>, H. WANG<sup>6</sup>, C. ZHANG<sup>3</sup>, D. ESTANDIAN<sup>2,5</sup>, M. DOMECILLO<sup>7</sup>, J. CHANG<sup>8</sup>, L. EVGENIOU<sup>8</sup>, A. CHOUEIRI<sup>2</sup>, S. WANG<sup>2,5,10</sup>, N. POLIZZI<sup>9</sup>, L. KIESSLING<sup>4,10,11</sup>, E. S. BOYDEN<sup>2,5,11,12,13</sup>,  
<sup>1</sup>Brain and Cognitive Sci., <sup>2</sup>MIT, Cambridge, MA; <sup>3</sup>MIT, Cambridge, MA, ; <sup>4</sup>Chem., MIT, Cambridge, MA; <sup>5</sup>McGovern Inst. for Brain Res., Cambridge, MA; <sup>6</sup>Scripps Res., Jupiter, FL, ; <sup>7</sup>Caltech, Pasadena, MA; <sup>8</sup>Harvard, Cambridge, MA; <sup>9</sup>Harvard, Boston, MA; <sup>10</sup>Broad Inst. of MIT and Harvard, Cambridge, MA; <sup>11</sup>Koch Inst., Cambridge, MA; <sup>12</sup>K. Lisa Yang Ctr. of Bionics and Yang Tan Collective, Cambridge, MA; <sup>13</sup>Howard Hughes Med. Inst., Cambridge, MA

**Abstract:** Proteins are central to many life processes, providing cellular structure, messengers, catalysts, receptors, switches, motors, and countless other functions. Their precise location, and organization with respect to each other, inform their function in biological systems such as the brain. Many proteins operate in scaffolded complexes, whose 3-d configuration governs their signaling polarity, kinetics, or qualitative outcome. Existing spatial protein mapping techniques either do not scale to the entire proteome, and/or exhibit limited spatial resolution and sensitivity. Here, we devise a method to combine expansion microscopy (ExM) with single-molecule protein sequencing chemistry. We show that an in-gel protocol of Edman degradation enables N-terminal amino acid degradation from peptides or proteins within ExM gels stabilized by post-expansion re-embedding. A binder (e.g., an engineered ClpS2 N-terminal amino acid binder, with enhanced specificity towards phenylalanine) can be used to read out the N-terminal amino acid of peptides that are processed via in-gel Edman degradation. In addition, commercially available antibodies for phenylalanine and valine, with high affinity kinetics, show specificity for their targets within ExM re-embedded gels. Our chemistry can be used immediately to facilitate in situ protein sequencing technology development along a number of dimensions and may serve as the backbone of future in situ protein sequencing platforms.



**Disclosures:** **C.M. Mitchell:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patents related to in situ protein sequencing. **S. Zoghi Tavana:** None. **C. Zhang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patents related to technologies discussed. **D. Estandian:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patents related to protein sequencing. **A. Choueiri:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patents related to protein sequencing. **S. Wang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SW is an inventor on several patents related to expansion microscopy.. **L. Kiessling:** None. **E.S. Boyden:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patents related to the technologies discussed..

## Poster

### PSTR250: Biochemical and Molecular Techniques II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.19/VV14

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** NIGMS R01GM139850-01  
NINDS U01NS128537

**Title:** Structure-guided engineering of a genetically encoded fluorescent opioid sensor for characterizing fentanyl pharmacology in vivo

**Authors:** \*L. TORP<sup>1</sup>, Y. WANG<sup>1</sup>, S. WAIT<sup>2</sup>, M. E. SODEN<sup>3</sup>, M. R. BRUCHAS<sup>4</sup>, A. BERNDT<sup>1</sup>;

<sup>1</sup>Bioengineering, <sup>2</sup>Mol. Engin., <sup>3</sup>Pharmacol., <sup>4</sup>Dept. of Anesthesiol. and Pain Med., Univ. of Washington, Seattle, WA

**Abstract:** Opioid-based analgesics are the most widely used treatments for chronic pain. However, opioid use and misuse have resulted in a national overdose crisis fueled by untreated opioid use disorder (OUD). Within the past decade, fentanyl has infiltrated the drug supply, leading to a rise in OUD cases and opioid overdose deaths. Fentanyl is a potent synthetic opioid and, like other exogenous opioids, binds to the  $\mu$ -opioid receptor ( $\mu$ OR), a G protein-coupled receptor. The  $\mu$ OR is expressed throughout many subcortical brain regions and regulates pain perception, reward, stress, and emotion. However, the pharmacological and spatiotemporal profile of fentanyl distribution in the brain is currently poorly understood. Traditional tools to monitor opioid accumulation in the brain often fall short in terms of sensitivity, specificity, and real-time kinetics. To address this need, the Berndt Lab developed  $\mu$ MASS, a genetically encoded  $\mu$ OR-based sensor that couples real-time opioid detection to an increased fluorescence response. However,  $\mu$ MASS detects both endogenous and exogenous opioids, making it difficult to discern the presence of specific ligands. We hypothesized this was due to  $\mu$ MASS recapitulating the native  $\mu$ OR's promiscuous ligand binding. As a solution, we tested whether structural analysis of  $\mu$ MASS-fentanyl binding may elucidate residues within the binding pocket governing specificity. We generated AlphaFold2  $\mu$ MASS models and docked fentanyl using AutoDock4, and observed fentanyl did not maintain a conserved bond within the opioid binding pocket. Introducing mutations in this region rendered  $\mu$ MASS specific only for fentanyl while greatly reducing affinity for endogenous opioid peptides, and we dubbed this sensor FentMASS1.0. This tool detects fentanyl *in vitro* in HEK293 cells and primary cortical neurons with nanomolar affinity. The fluorescence signal is rapid and reverses upon application of  $\mu$ OR antagonist naloxone. To enhance FentMASS1.0 signal we introduced  $\mu$ OR receptors from alternative species and applied homologous mutations to each sensor. This resulted in FentMASS2.0 which demonstrated increased dynamic range while maintaining fentanyl specificity. Ultimately, this sensor will enable cell-type specific fentanyl pharmacokinetics measurements to determine if there are appreciable differences in the timing, accumulation, and potency of fentanyl across  $\mu$ OR-positive brain regions. *In vivo* experiments can determine fentanyl pharmacokinetics in the brain during various stages of fentanyl use and OUD development to directly link real-time pharmacology to behavioral phenotypes in freely behaving animals.

**Disclosures:** L. Torp: None. Y. Wang: None. S. Wait: None. M.E. Soden: None. M.R. Bruchas: None. A. Berndt: None.

**Poster**

## **PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.20/VV15

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Support:** NIGMS R01GM139850-01  
NINDS UONS128537

**Title:** High-throughput engineering of genetically encoded  $\mu$ -opioid sensors with enhanced sensitivity and neuronal expression for detecting opioids *in vivo*

**Authors:** \*Y. WANG<sup>1</sup>, L. TORP<sup>2</sup>, S. WAIT<sup>3</sup>, M. E. SODEN<sup>4</sup>, M. R. BRUCHAS<sup>5</sup>, A. BERNDT<sup>2</sup>;

<sup>2</sup>Bioengineering, <sup>3</sup>Mol. Engin., <sup>4</sup>Pharmacol., <sup>5</sup>Dept. of Anesthesiol. and Pain Med., <sup>1</sup>Univ. of Washington, Seattle, WA

**Abstract:** Genetically encoded fluorescent indicators (GEFIs) are powerful tools for real-time monitoring of neural activities, enabling high sensitivity, specificity, and spatiotemporal resolution. Engineering GEFIs has become a primary goal for many seeking to understand neuromodulation. However, it is challenging to study opioid signaling due to the vast mutational landscape of large G protein-coupled receptors (GPCRs) like the  $\mu$ -opioid receptor ( $\mu$ OR). To address this problem, the Berndt Lab developed the optogenetic microwell array screening system (Opto-MASS), a high-throughput screening platform capable of screening thousands of  $\mu$ OR-based GEFIs in a single day. Using Opto-MASS, we previously leveraged to identify an improved opioid sensor  $\mu$ MASS, which displays an increased fluorescence response to endogenous (met-enkephalin) and exogenous (fentanyl) opioid ligands.  $\mu$ MASS exhibits an EC<sub>50</sub> of 219 nM for met-enkephalin and 255 nM for fentanyl in HEK293 cells. To further improve the baseline fluorescence, signal-to-noise ratio, and opioid selectivity of  $\mu$ MASS, we generated cross-species sensor variants by incorporating  $\mu$ OR sequences from alternative species. This resulted in  $\mu$ MASS1.5 and  $\mu$ MASS1.7.  $\mu$ MASS1.5 showed  $\sim$ 1.8-fold increase in fluorescence response to 10  $\mu$ M fentanyl compared to  $\mu$ MASS, while  $\mu$ MASS1.7 achieved the strongest response with a  $\sim$ 2.3-fold increase.  $\mu$ MASS1.7 also displayed improved EC<sub>50</sub> values for both met-enkephalin and fentanyl (e.g., fentanyl EC<sub>50</sub> 123 nM for  $\mu$ MASS1.7 vs. 255 nM for  $\mu$ MASS). In primary rat cortical neurons,  $\mu$ MASS1.5 showed a  $\sim$ 1.5-fold increase in  $\Delta F/F_0$  over  $\mu$ MASS to met-enkephalin, whereas  $\mu$ MASS1.7 showed a  $\sim$ 2-fold increase. To further improve neuronal expression, we systematically tested membrane localization and trafficking tags. Incorporating these motifs resulted in a  $\sim$ 1.8-fold increase in fluorescence and enhanced membrane expression in neurons compared to  $\mu$ MASS, with  $\mu$ MASS2.0 emerging as the top-performing variant for *in vivo* neural applications. These advancements establish a framework for engineering next-generation opioid sensors with improved sensitivity and specificity. Taken together, we leveraged the high-throughput capabilities of Opto-MASS to engineer novel tools to detect opioids in real-time. We are currently applying these sensors *in vivo* to explore the spatial and temporal regulation of opioid peptides in freely behaving animals, providing critical insights into the neuromodulatory roles of endogenous opioid signaling across different brain regions.

**Disclosures:** Y. Wang: None. L. Torp: None. S. Wait: None. M.E. Soden: None. M.R. Bruchas: None. A. Berndt: None.

## **Poster**

### **PSTR250: Biochemical and Molecular Techniques II**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.21/VV16

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Title:** Machine learning-guided engineering of red-shifted genetically encoded calcium indicators

**Authors:** \*S. Li<sup>1</sup>, S. WAIT<sup>2</sup>, Y. WANG<sup>1</sup>, L. TORP<sup>1</sup>, H. DANA<sup>3</sup>, A. BERNDT<sup>1</sup>;

<sup>1</sup>Dept. of Bioengineering, <sup>2</sup>Mol. Engin., Univ. of Washington, Seattle, WA; <sup>3</sup>Dept. of Neurosciences, Lerner Res. Inst., Cleveland, OH

**Abstract:** Genetically encoded calcium indicators (GECIs) provide an essential method in neuroscience to monitor neuron activation *in vivo*. To meet different experimental requirements, GECIs' biophysical characteristics can be altered by mutations. However, current red GECIs suffer from limitations such as low brightness, slow kinetics, and poor photostability, which restrict their application in deep brain region imaging. Furthermore, labor-intensive site-saturation mutagenesis approaches have largely constrained sensor engineering efforts, yielding only modest enhancements in sensor responsiveness. To efficiently engineer these sensors, the Berndt Lab previously reported a machine-learning pipeline that was trained on publicly available datasets of mutational effects of multiple GECIs (Wait et al. 2024). This ensemble algorithm learns complex sequence-functional relationships and nominates potential variants from saturation mutation predictions. Here, we used this platform to optimize two red-shifted calcium indicators (Ex./Em.: 580 nm/605 nm), jRCaMP1b and jRGECO1a. We have identified novel variations that demonstrate faster kinetics, enhanced baseline fluorescence, and superior sensitivity compared to the base constructs in primary rat cortical neurons. For jRCaMP1b, a specific single mutation exhibited over a 2-fold increase in  $\Delta F/F_0$  at 1 action potential (AP), 10 APs, and 80 APs. Another variant of jRGECO1a showed a 1.25-fold augmentation in dynamic range. Additionally, we also validated these potential variations *in vivo*. Furthermore, the mutations identified by the machine learning method can be structurally mapped to reveal critical intramolecular interactions that contribute to the improved biophysical capabilities. Those mutations predominantly clustered at the interface between calmodulin and the calcium-binding peptide, as well as between the fluorescent protein and calmodulin, indicating potential hotspots for functional tuning. Together, these findings not only support data-driven protein engineering effectively promoting the optimization of GECIs but also offer new and promising tools for the real-time monitoring of deep tissue.

**Disclosures:** S. Li: None. S. Wait: None. Y. Wang: None. L. Torp: None. H. Dana: None. A. Berndt: None.

## Poster

### PSTR250: Biochemical and Molecular Techniques II

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR250.22/VV17

**Topic:** J.01. Molecular, Biochemical, and Genetic Techniques

**Title:** Engineering a protein-based fluorescent sensor for real-time monitoring of estradiol in the brain.

**Authors:** \*A. MOGHADASI<sup>1</sup>, J. H. LEE<sup>2</sup>, M. TRZECIAK<sup>3</sup>, V. CHAVAN<sup>1</sup>, M. WITT<sup>1</sup>, G. D. STUBER<sup>4</sup>, A. BERNDT<sup>1</sup>;

<sup>1</sup>Bioengineering, <sup>2</sup>Bioengineering / MoES PhD, <sup>4</sup>Pharmacol., <sup>3</sup>Univ. of Washington, Seattle, WA

**Abstract:** The intricate roles of sex steroids in human physiology extend far beyond their traditional associations with reproductive function, affecting areas in cardiovascular health, bone density, metabolism, and cancer progression. In the brain, neurosteroids like estrogens are both synthesized locally and can target the brain from peripheral organs. They play various neuromodulatory roles, influencing synaptic plasticity, cognitive processes, and behavior. Despite their significance, tissue- and cell-type-specific studies of steroids in vivo remain challenging due to the absence of tools capable of tracking steroid dynamics with spatio-temporal resolution. Optical tools enable the detailed characterization of steroid release, dynamics, and signaling in the brain across different physiological and disease-relevant contexts. Here we present eNOVA, a genetically encoded fluorescent sensor for real-time monitoring of estradiol (E2). The in-vitro characterization of the sensor in HEK cells demonstrated a 180% dynamic fluorescence increase in response to E2 stimulation at saturating concentrations, sensitivity to concentrations as low as the nanomolar range, and estrogen-specificity. We also observed similar biophysical properties when the sensor was expressed in primary rat cortical neurons. Furthermore, we performed stereotactic injection of AAV1-DIO vector containing the sensor into the medial preoptic area of the hippocampus in Cre-ESR1 mice, where we further validated the sensor's compatibility in the brain through 2-photon imaging of ex-vivo brain slices and fiber photometry in-vivo. The estrous cycle in mice spans approximately four days, requiring tools capable of long-term and non-continuous monitoring of E2 fluctuations in the brain. To address this, we engineered a ratiometric sensor variant by integrating a red fluorescent protein (RFP) to serve as a reference point. This design enables normalization of signal variation, which may result from expression variability, photobleaching, or motion artifacts. Upon validating the applicability of this variant, we confirmed that RFP fluorescence remains stable and unresponsive to E2 stimulation, serving as a reliable control. This first-in-class sensor offers promising potential for visualizing and investigating estrogen signaling in the brain. By enabling the real-time monitoring of estrogen with high spatio-temporal resolution, it also provides a powerful platform for exploring broader biological questions, including the regulatory roles of estrogen in maintaining homeostasis, mediating brain-body communication, and influencing disease progression.

**Disclosures:** **A. Moghadasi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a provisional patent for the sensor design. **J.H. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a provisional patent for the sensor design. **M. Trzeciak:** None. **V. Chavan:** None. **M. Witt:** None. **G.D. Stuber:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a provisional patent for the sensor design. **A. Berndt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a provisional patent for the sensor design.

## **Poster**

### **PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.01/VV18

**Topic:** J.04. Physiological Methods

**Title:** Minimally invasive, wide-field two-photon imaging of the brainstem and nucleus tractus solitarii at cellular resolution

**Authors:** \***A. HATAKEYAMA**<sup>1,2</sup>, **D. YAMADA**<sup>1</sup>, **H. KUNIISHI**<sup>3</sup>, **C. ITO**<sup>2</sup>, **E. TAKEUCHI**<sup>4</sup>, **S. TSUJI**<sup>5</sup>, **M. TSUTSUMI**<sup>6,8</sup>, **T. ICHIKI**<sup>9</sup>, **K. OTOMO**<sup>8,6,10</sup>, **T. YOSHIOKA**<sup>1</sup>, **T. KOBAYASHI**<sup>5</sup>, **A. NORITAKE**<sup>7</sup>, **Y. AOKI**<sup>4</sup>, **T. NEMOTO**<sup>6,8</sup>, **H. YUKAWA**<sup>2</sup>, **A. SAITOH**<sup>1</sup>, **J. NABEKURA**<sup>5</sup>, **M. SEKIGUCHI**<sup>1,4</sup>, **M. AGETSUMA**<sup>1,2,5</sup>;

<sup>1</sup>Lab. of Pharmacology, Fac. of Pharmaceut. Sci., Tokyo Univ. of Sci., Tokyo, Japan; <sup>2</sup>Inst. for Quantum Life Sci., Natl. Inst. for Quantum Sci. and Technol., Chiba, Japan; <sup>3</sup>Div. of Develop. of Mental Functions, Res. Ctr. for Child Mental Develop., Univ. of Fukui, Yoshida-gun, Fukui, Japan; <sup>4</sup>Dept. of Mol. Therapy, Natl. Ctr. of Neurol. and Psychiatry, Kodaira, Japan; <sup>5</sup>Natl. Inst. for Physiological Sciences, Dept. of Homeostatic Regulation, <sup>6</sup>Natl. Inst. for Physiological Sciences, Div. of Biophotonics, <sup>7</sup>Natl. Inst. for Physiological Sciences, Div. of Behavioral Develop., Natl. Inst. of Natural Sci., Okazaki, Japan; <sup>8</sup>Biophotonics Res. Group, The Exploratory Res. Ctr. on Life and Living Systems, Okazaki, Japan; <sup>9</sup>Grad. Sch. of Med. and Dent. Sci., Niigata Univ., Niigata, Japan; <sup>10</sup>Grad. Sch. of Med., Juntendo Univ., Tokyo, Japan

**Abstract:** Brain-viscera communication plays a crucial role in regulating mental health, with the vagus nerve being a key structure mediating this interaction. Clinically, artificial vagus nerve stimulation (VNS) is used to treat various neuropsychiatric disorders, highlighting the importance of vagal afferent fibers in regulating emotion. The nucleus tractus solitarii (NTS) is a brainstem structure proposed to receive signals from vagal afferents and relay them to brain networks for emotion regulation. However, due to its deep location below the cerebellum and proximity to vital brain regions, the specific mechanisms by which the NTS integrates and processes VNS or other multisensory inputs from peripheral organs for emotion regulation

remain unclear. To address these questions, here we developed an in vivo two-photon imaging technique using a prism-based optical interface (Double-Prism based brainStem imaging under Cerebellar Architecture and Neural circuits, "D-PSCAN"). The D-PSCAN method enables the observation of neural population activity at single-cell resolution in the wide brainstem areas, including the NTS, while largely preserving the overlying cerebellum, a region also implicated in emotion regulation. It distinguishes NTS activity from descending vagus neurons located ventrally. The recorded neural activity data were analyzed to evaluate the physiological characteristics of NTS neurons, such as their responsiveness to VNS. We found variability in response properties among individual neurons within the NTS. Changes in neuronal responsiveness were observed with repeated VNS, showing either enhancement or attenuation depending on the specific stimulation frequencies and intensities. We also applied this technique to study responses to cholecystokinin-8 (CCK), a gastrointestinal hormone that serves as a more physiological stimulus than VNS. Our results suggest the applicability of this method for detailed understanding of the physiological mechanism of the NTS and future research on emotional regulation through the vagus-NTS pathway.

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## **Poster**

### **PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.02/VV19

**Topic:** J.04. Physiological Methods

**Support:** Stanford Knight Initiative for Brain Resilience

**Title:** Tru-fact: a general method for aligning in vivo recordings of neural activity with spatial biology and anatomic datasets at single cell resolution

**Authors:** L. WANG<sup>1</sup>, \*X. JIANG<sup>1</sup>, X. SUN<sup>1</sup>, G. CHATTREE<sup>2</sup>, A. CETIN<sup>1</sup>, X. CAI<sup>1</sup>, R. T. CHRAPKIEWICZ<sup>1</sup>, O. HERNANDEZ<sup>1</sup>, F. DINC<sup>1</sup>, Y. ZHANG<sup>1</sup>, M. J. SCHNITZER<sup>3</sup>;

<sup>2</sup>Dept. of Neurol. & Neurolog. Sci., <sup>1</sup>Stanford Univ., Palo Alto, CA; <sup>3</sup>Depts. Biol. & Applied Physics, Stanford University, Dept. of Biol., Stanford, CA

**Abstract:** State-of-the-art imaging methods can monitor the activity of hundreds to tens of thousands of individual neurons, while spatial biology techniques offer rich profiles of individual cells' molecular attributes. Yet, a critical gap remains, as we lack reliable methods to align cells monitored in the live brain with their transcriptomic or proteomic features determined *post*



*mortem* with spatial biology methods. Bridging this gap is essential to understand how neural dynamics and cellular function are shaped by neurons' cell-type identities, gene expression patterns, connectivity, and molecular states.

We present **TRU-FACT** (Total Registration Under Functional Activity, Connectivity, and Transcriptomics), a reliable, scalable, and economical method to align *in vivo* neural imaging datasets with the same cells' molecular attributes imaged *ex vivo*. For this registration, TRU-FACT combines precise mechanical alignments with a computational metric of alignment fidelity. Using TRU-FACT, we registered neural activity patterns in awake behaving animals to transcriptomic and projectomic features of the same individual cells.

We first verified that TRU-FACT provides accurate alignments even with densely labeled sets of neurons, as validated using ground-truth fiducial markers. This involves an algorithm, termed Soma-print, to automate alignments. We applied TRU-FACT across multiple imaging modalities—including with large objective lenses with curved fields of view, GRIN lenses, and prisms—highlighting its flexibility and robustness. To expand our capabilities for molecular and anatomical profiling, we integrated into TRU-FACT retro-AAV barcoding, to map cells' axonal projections, and performed transcriptomic analyses with multi-round low-plex or high-plex RNA fluorescence *in situ* hybridization (RNA FISH). As a practical demonstration, we used TRU-FACT to examine gene expression and long-range projection patterns of mouse layer 5 motor cortical neurons activated during a grasping behavior, showcasing the method's utility for functional dissections of precisely defined neural subtypes.

Overall, TRU-FACT provides a unified framework for aligning *in vivo* recordings of neural activity to *ex vivo* molecular profiles that can be obtained via a wide range of spatial transcriptomic, spatial proteomic, and connectomic tracing methods. By integrating functional, molecular, and anatomical information at single-cell resolution, TRU-FACT opens new avenues for uncovering cellular and network mechanisms underlying brain function and dysfunction, with transformative potential for both basic neuroscience and therapeutic discovery.

**Disclosures:** **L. Wang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stanford University. **X. Jiang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stanford University. **X. Sun:** None. **G. Chattree:** None. **A. Cetin:** None. **X. Cai:** None. **R.T. Chrapkiewicz:** None. **O. Hernandez:** None. **F. Dinc:** None. **Y. Zhang:** None. **M.J. Schnitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stanford University.

## **Poster**

### **PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.03/VV20

**Topic:** J.04. Physiological Methods

**Support:** Howard Hughes Medical Institute

**Title:** Tracker: iterative cell extraction and registration for analysis of time-lapse neural calcium imaging datasets

**Authors:** \*O. HAZON<sup>1</sup>, T. TASCI<sup>1</sup>, Y. LI<sup>2</sup>, A. SHAI<sup>1</sup>, A. J. CHRISTENSEN<sup>5</sup>, T. H. KIM<sup>1</sup>, O. JAIDAR<sup>3</sup>, T. ROGERSON<sup>1</sup>, F. DINC<sup>6</sup>, R. T. CHRAPKIEWICZ<sup>1</sup>, M. J. SCHNITZER<sup>4</sup>;  
<sup>2</sup>Biol., <sup>3</sup>Neurosurg., <sup>4</sup>Depts. Biol. & Applied Physics & Neurosurg., <sup>1</sup>Stanford Univ., Stanford, CA; <sup>5</sup>Neurosci., WUSTL Sch. of Med., St. Louis, MO; <sup>6</sup>Kavli Inst. for Theoretical Physics, UC Santa Barbara, Santa Barbara, CA

**Abstract:** Techniques for large-scale neural calcium imaging have enabled longitudinal recordings of ensemble neural dynamics across repeated imaging sessions over days to months. To assess how neural activity patterns evolve over the span of these time-lapse studies, one typically must track individual neurons' identities across multiple imaging sessions. However, computational approaches to accurately identify and track neurons have generally relied on heuristic methods. Here we introduce a computational framework termed TRACKER (Time-lapse Registration And Cell Extraction Routine) for extracting and tracking cells' identities across long-term calcium imaging studies with high reliability. We combine image registration techniques with a graph theoretic clustering algorithm to identify likely sets of cell filters from different sessions that correspond to the same physical cell. After establishing cell identities, TRACKER can detect neurons that the cell extraction procedure initially overlooked in the video data from some sessions but that are predicted to be present. This boosting of cell counts is achieved by re-initializing the cell extraction routine using a combined cell map, aggregated across all imaging sessions. On simulated and experimental longitudinal data, TRACKER provides substantial gains in the numbers of detected neurons and the accuracy of cell registration. We tested TRACKER on diverse one-photon and two-photon fluorescence calcium imaging datasets from awake behaving rodents, which were imaged over periods spanning weeks to months. The largest of our datasets comprises up to 80 imaging sessions per animal, acquired over a period of 6 months. To evaluate TRACKER against conventional approaches to cell extraction that use the data from individual imaging sessions, we measured the total numbers of cells detected in time-lapse imaging datasets and found 13%-97% more cells using TRACKER. We also found that the use of TRACKER improves the accuracy of neural ensemble decoders trained to output behavioral parameters. Overall, TRACKER provides an efficient, scalable, and flexible approach to the analysis of time-lapse neural calcium imaging data that improves the total counts of extracted neurons and the results of subsequent biological analyses.

**Disclosures:** O. Hazon: None. T. Tasci: None. Y. Li: None. A. Shai: None. A.J. Christensen: None. T.H. Kim: None. O. Jaidar: None. T. Rogerson: None. F. Dinc: None. R.T. Chrapkiewicz: None. M.J. Schnitzer: None.

**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.04/VV21

**Topic:** J.04. Physiological Methods

**Support:** Burroughs Wellcome Fund (CASI 1015761)  
National Science Foundation (CAREER 1847141)  
National Institute of Neurological Disorders and Stroke (R01NS118289)  
National Eye Institute (R01NS118289)

**Title:** Adaptive line-excitation for high-speed two-photon microscopy

**Authors:** Y. LI<sup>1</sup>, S. GUO<sup>1</sup>, B. MATTISON<sup>1</sup>, J. HU<sup>1</sup>, K. MAN<sup>2</sup>, \*W. YANG<sup>1</sup>;

<sup>1</sup>Univ. of California Davis, Davis, CA; <sup>2</sup>Max Planck Florida Inst. for Neurosci., Jupiter, FL

**Abstract:** Two-photon fluorescence microscopy is a powerful technique for recording neuronal activity in live animals. In conventional setups, the microscope repeatedly performs raster scanning of a single diffraction-limited spot across the sample's field of view (FOV), and constructs each frame pixel by pixel. While effective, this method is inherently slow and can expose brain tissue to excessive light, which increases the risk of photodamage. To address these limitations, we developed a high-speed two-photon microscope capable of imaging neural activity at cellular resolution. Our system employs a short-line illumination combined with an adaptive sampling strategy to significantly enhance the imaging speed while reducing the total laser power delivered to the brain. By integrating a digital micromirror device (DMD) in the two-photon microscope, we selectively illuminate only the regions of interest (ROIs). The DMD is located at a conjugate plane of the sample, and encodes the spatial locations and morphologies of the ROIs (i.e. neuronal cell bodies). The DMD can thus spatially modulate the excitation light, and ensure only the ROIs are illuminated. Furthermore, rather than scanning a diffraction-limited spot, we shape the excitation beam into a short line, which can simultaneously sample larger portions of the ROIs. This adaptive line-excitation approach increases the imaging speed by a factor of 5-10 and reduces the overall laser exposure on the brain tissue by more than tenfold compared to the traditional point-scanning methods. Using this technique, we achieved high-speed in vivo imaging of neuronal activity in the mouse cortex at frame rates up to 198 Hz. Our microscope introduces a novel sampling paradigm for laser-scanning two-photon microscopy and offers a powerful platform for high-throughput neural activity imaging.

**Disclosures:** Y. Li: None. S. Guo: None. B. Mattison: None. J. Hu: None. K. Man: None. W. Yang: None.

**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.05/VV22

**Topic:** J.03. Anatomical Methods

**Support:** NIH Grant RF1MH123402  
NIH Grant RF1MH133764  
NIH Grant RF1MH124611  
University of Michigan Rackham Predoctoral Fellowship

**Title:** A parallelly distributed microscope and software system for scalable high-throughput multispectral 3D imaging.

**Authors:** \***L. A. WALKER**<sup>1</sup>, H. JIANG<sup>2</sup>, Y. LI<sup>4</sup>, B. DUAN<sup>4</sup>, X. NIU<sup>4</sup>, J.-C. HSIEH<sup>4</sup>, M.-C. CHENG<sup>4</sup>, H. SU<sup>5</sup>, K. SHENG<sup>6</sup>, J. TANG<sup>4</sup>, K. ATHUKORALA<sup>4</sup>, S. GREENE<sup>7</sup>, R. PAN<sup>8</sup>, A. PARLAPALLI<sup>9</sup>, P. YIN<sup>6</sup>, M. CUI<sup>3</sup>, D. CAI<sup>4</sup>;

<sup>1</sup>The Univ. of Michigan, Ann Arbor, MI; <sup>2</sup>ECE, <sup>3</sup>Purdue Univ., West Lafayette, IN; <sup>4</sup>Univ. of Michigan, Ann Arbor, MI; <sup>5</sup>Harvard, Cambridge, MA; <sup>6</sup>Harvard Univ., Cambridge, MA; <sup>7</sup>Univ. of Michigan, Ann Arbor, MI; <sup>8</sup>New Trier High Sch., Winnetka, IL; <sup>9</sup>Washtenaw Intl. High Sch., Ypsilanti, MI

**Abstract:** High-throughput microscopy is an essential tool for interrogating the structure and function of neural tissues. Recent advances in microscope design have broadened this horizon, but many designs have essential compromises between resolution, imaging depth, color channel density, and acquisition speed. In this poster, we will discuss our recent advances in designing a parallel-line scanning confocal microscope (plSCM) which can achieve 180 nm x 220 nm x 650 nm resolution across a 2 mm imaging depth. Novel optical designs enable minimal laser astigmatism, resulting in more efficient line excitation. By spatially separating the excitation laser lines, the plSCM allows simultaneous collection of 3 channel images using three separate but synchronized cameras, while omitting spectral crosstalk. To handle a 1.1 image gigavoxels per second data throughput, we have developed a Scalable Network-Distributed Imaging Framework (SNDiF) to control the continuous, full-speed acquisition of images, while they are transferred over the network to a supercomputer for storage. The performance of sustained imaging was demonstrated by a continuous collection of a single dataset that is >300 TB with an effective voxel size of ~30 nm x 30 nm x 70 nm. Neuron tracing on Bitbow-labeled Drosophila brain reveals stereotypic serotonergic neurons that can be identified from the Flywire EM-connectome, showing the value of the plSCM system for large-scale connectomics studies. Finally, we will show how the plSCM principles can be extended to include greater than three spectral channels to allow increasingly spectrally-dense microscopy.

**Disclosures:** **L.A. Walker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Application 18378485. **H. Jiang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent 12135411B2. **Y. Li:** None. **B. Duan:** None. **X. Niu:** None. **J. Hsieh:** None. **M. Cheng:** None. **H. Su:** None. **K. Sheng:** None. **J. Tang:** None. **K. Athukorala:** None. **S. Greene:** None. **R. Pan:** None. **A. Parlapalli:** None. **P. Yin:** None. **M. Cui:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent 12135411B2. **D. Cai:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Application 18378485.

**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.06/WW1

**Topic:** J.04. Physiological Methods

**Title:** Simultaneous pan-cell-type recording of cortical dynamics across conscious states with OSCA

**Authors:** \*F. XIN<sup>1</sup>, Y. GAO<sup>1</sup>, K. YUAN<sup>2</sup>;

<sup>1</sup>Tsinghua Univ., Beijing, China; <sup>2</sup>Tsinghua Univ., Beijing City, China

**Abstract:** Consciousness emerges from intricate neural activities, which involves the coordinated interplay of diverse cell types and their constantly evolving dynamics. While network-level macroscale phenomena (e.g. heightened cortical synchrony and rhythm oscillations during unconsciousness) are well-documented, existing single-cell-resolution methods, relying on genetic calcium indicators in transgenic mouse, can monitor only one or two cell types simultaneously. Comprehensively tracking single-neuron activity across all major cortical neuron types under different conscious states and definitively identifying each recorded neuron's cell type remain unachievable. Here we introduce **OSCA (Omni-Single-Capture Activities)**, a novel technology overcoming this barrier by integrating in vivo neural activity imaging, ex vivo cell-type phenotyping, and cross-modal registration. Specifically, OSCA combines: unbiased single-neuron activity imaging via two-photon synthetic aperture microscopy, high-quality three-dimensional structural imaging achieved through multicolor volumetric cell-type phenotyping with VIVIT tissue clearing, and spectral unmixing algorithms coupled with in vivo-to-ex vivo 3D structural registration algorithm for one-to-one cell-type identification. This integrated approach achieves pan-cell-type neural activity recording. Applying OSCA to visual and retrosplenial cortices in naturally awake and isoflurane-anesthetized mice, we simultaneously recorded activities of over 1,000 neurons spanning more than 10 distinct cell types across L1 to L6 within a single animal. Leveraging this dataset with neural dynamics modeling, we investigated computational mechanisms within the cortex underlying different conscious states. OSCA represents the first demonstration of simultaneous, cell-type-resolved monitoring of single-neuron activity across virtually all major cortical cell types in vivo during distinct conscious states, overcoming a fundamental limitation in systems neuroscience to enable direct investigation of cell-type-specific ensemble dynamics underpinning complex brain functions.

**Disclosures:** F. Xin: None. Y. Gao: None. K. Yuan: None.

**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.07/WW2

**Topic:** J.04. Physiological Methods

**Support:** STI2030-Major Projects, grant no. 2022ZD0204600  
National Natural Science Foundation of China, grant no. U1909205

**Title:** A 40MHz femtosecond laser repetition frequency divider for enhanced two-photon imaging

**Authors:** \*S. TANG<sup>1,2,3,4,5</sup>;

<sup>1</sup>Peking Univ., Beijing, China; <sup>2</sup>Peking Univ. Sch. of Life Sci., Beijing, China; <sup>3</sup>Peking-Tsinghua Ctr. for Life Sci., Beijing, China; <sup>4</sup>IDG/McGovern Inst. for Brain Res. at Peking Univ., Beijing, China; <sup>5</sup>Key Lab. of Machine Perception (Ministry of Education), Peking Univ., Beijing, China

**Abstract:** We present a simplified femtosecond laser repetition frequency divider designed to divide an 80MHz repeated laser pulse into a 40MHz laser pulse through a Pockels cell working in a resonant model. The driver electronics include a electronic frequency divider, power amplifier and impedance transformer, which can be custom built. By simply integrating this devices into a conventional two-photon imaging system, we observed a two-fold increase in two-photon excitation efficiency and imaging intensity with same average excitation laser power.

**Disclosures:** S. Tang: None.

## **Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.08/WW3

**Topic:** J.03. Anatomical Methods

**Support:** NIH R34 NS116733  
NIH R01 EY018839  
NIH R21 EY025828  
NIH P51 OD010425  
NIH U01 NS115585  
NIH R01 EY 010115  
NIH UG3 MH126864

**Title:** Effective attenuation length quantification of in vivo multi-photon imaging in non-human primate

**Authors:** \*G. HATANAKA<sup>1</sup>, K. TAKASAKI<sup>2</sup>, S. CHATTERJEE<sup>2</sup>, T. KIM<sup>1</sup>, C. DYLLA<sup>1</sup>, A. K. PASUPATHY<sup>1</sup>, R. REID<sup>2</sup>, J. WATERS<sup>2</sup>, W. BAIR<sup>1</sup>;

<sup>1</sup>Univ. of Washington, Seattle, WA; <sup>2</sup>Allen Inst. for Brain Sci., Seattle, WA

**Abstract:** In multi-photon imaging, the penetration depth is constrained by the attenuation of excitation light due to absorption and scattering in optically dense biological tissues. Quantifying the effective attenuation length in multi-photon imaging is critical for optimizing how deeply, safely, and clearly we can visualize brain structures and monitor neural activity. While attenuation lengths have been characterized in rodents, data in non-human primates (NHPs), whose thicker cortical structure requires greater imaging depth, remain scarce. In this study, we performed in vivo three-photon fluorescence imaging (TPFI) and third-harmonic generation imaging (THGI) in an anesthetized non-human primate (NHP) using a 1300 nm excitation wavelength (Monaco and Opera F, Coherent Inc.). To provide a fluorescent target for TPFI, FITC-dextran was intravenously injected to label the cortical vasculature. We acquired image stacks from the cortical surface to depths of up to 800  $\mu\text{m}$  with 2  $\mu\text{m}$  steps. Fluorescence and third-harmonic signals were separated with a 488 nm dichroic mirror and collected simultaneously using individual photomultiplier tubes. Imaging was conducted using two objective lenses: a 25 $\times$ , 2 mm working distance (WD) water-immersion lens (XLPLN25XWMP2, Olympus) and a 10 $\times$ , 20 mm WD air-immersion lens (Cousa objective, Pacific Optica). Capillaries were visible up to 500  $\mu\text{m}$  with the water-immersion lens and 200  $\mu\text{m}$  with the air-immersion lens using less than 50 mW of laser power. We analyzed depth-dependent signal intensities at varying excitation powers and fitted their decay to an exponential function to estimate the effective attenuation length. Using a water-immersion lens, the estimated effective attenuation lengths were 221  $\mu\text{m}$  for TPFI and 173  $\mu\text{m}$  for THGI within the 0-400  $\mu\text{m}$  depth range. With an air-immersion lens, the corresponding values were 98  $\mu\text{m}$  and 105  $\mu\text{m}$ , respectively, within the range of 0-300  $\mu\text{m}$ . These results demonstrate the capability of deep cortical imaging in non-human primates using three-photon microscopy up to 500  $\mu\text{m}$  depth under relatively low laser power. The shorter effective attenuation length observed with the air-immersion objective lens may be explained by the increasing proportion of tissue relative to air within the working distance as the focal depth increases, potentially enhancing absorption of the excitation light. By quantifying light attenuation in both TPFI and THGI, our study provides important benchmarks for optimizing optical system design and advancing deep-brain imaging in large animal models.

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## **Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #: PSTR251.09/WW4**

**Topic:** J.08. Methods to Modulate Neural Activity

**Support:** European research Council ERC2019-ADG-885090  
French National research Agency ANR-18-IAHU-01, IHU FOReSIGHT  
European Research Council Horizon 2020 H2020-ICT (DEEPER,  
101016787)

**Title:** Three-photon holographic microscopy for deep precise optogenetics

**Authors:** C. TELLIEZ, A. MOHAMED LAFIRDEEN, J. NATAF, T. UNG, R. CASTILLO  
NEGRETE, C. GRIMM, E. RONZITTI, V. ZAMPINI, \*E. PAPAGIAKOUMOU, V.  
EMILIANI;  
Inst. de la Vision, Paris, France

**Abstract:** Optogenetics—the use of light to control genetically modified neurons—has transformed neuroscience by allowing highly specific manipulation of neuronal circuits. While single-photon widefield illumination approaches allow reliable activation or inhibition of specific neurons expressing optogenetic tools, they lack spatial precision. Two-photon (2P) optogenetics, combined with 2P imaging, has significantly improved spatial precision and enabled near single-cell resolution in vivo, but remains limited in penetration depth to few hundreds of micrometers, due to scattering. Although endoscopic methods extend the reach of 2P techniques, they are invasive and less suited for small or delicate organisms.

Three-photon (3P) excitation microscopy using longer wavelengths (typically 1300-1700 nm) offers deeper tissue penetration and reduced scattering, making it a promising alternative for functional interrogation of deep brain regions. Despite its widespread use in structural and functional imaging, 3P optogenetic activation has remained largely unexplored, with only one prior demonstration in cultured cells.

Here, we present the first in-depth validation of 3P optogenetics in vivo at depths up to 800  $\mu\text{m}$  in the mouse visual cortex. We also present a rigorous characterization of 3P optogenetic activation in organotypic brain slices, targeting three excitatory and one inhibitory opsin. Using Computer-Generated Holography (CGH) and temporal focusing (TF), we achieved soma-targeted activation with 1300 nm or 1700 nm illumination, confirming that the induced photocurrents followed a 3P excitation regime and elicited reliable neuronal responses. Notably, we show enhanced spatial confinement and reduced out-of-focus activation compared to 2P stimulation, with near single-cell resolution. This new method, combining the depth penetration of 3P excitation with the spatial precision of holographic techniques, opens new avenues for probing deep neural circuits with unprecedented precision.

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**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM



**Program #/Poster #:** PSTR251.10/WW5

**Topic:** J.03. Anatomical Methods

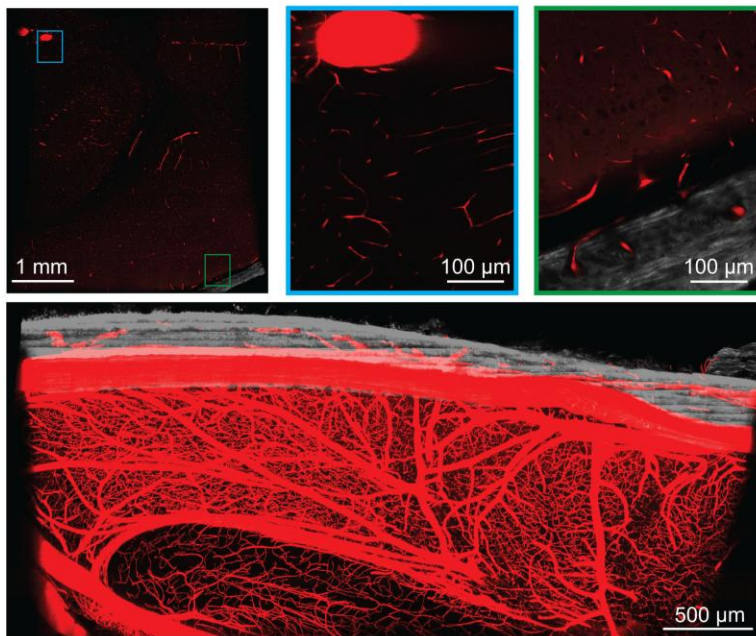
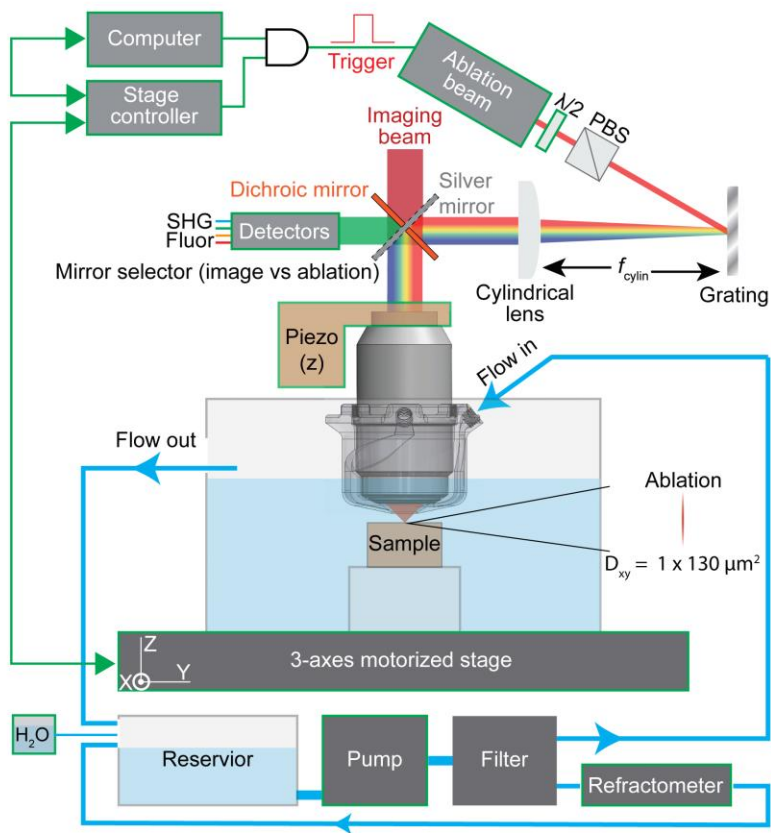
**Support:** NIH U19 NS123717  
NIH R35 NS097265  
American Heart Association 906077

**Title:** Spatiotemporal focusing enables all-optical in situ histology of heterogeneous tissue

**Authors:** \*S. HUANG<sup>1</sup>, X. JI<sup>1</sup>, B. FRIEDMAN<sup>2</sup>, D. KLEINFELD<sup>1,3</sup>;

<sup>1</sup>Dept. of Physics, <sup>2</sup>Dept. of Computer Sci. and Engin., <sup>3</sup>Dept. of Neurobio., Univ. of California San Diego, San Diego, CA

**Abstract:** Sub-micrometer, brain-wide reconstructions of the cerebrovascular network are essential for understanding and predicting how local changes to vascular tone or single-vessel occlusions propagate to global perfusion patterns. Mechanical sectioning techniques cannot simultaneously cut mineralized skull and adjacent soft parenchyma, so brains must be excised, tearing surface vessels and obliterating the brain-skull interface in the process. Alternatively, bone can be decalcified, but this may lead to differential shrinkage of tissue and shearing at tissue interfaces. While femtosecond Gaussian-focused laser ablation has been successfully used to ablate both bone and soft tissue, a point-by-point tissue removal scheme is impractical for scaling up to the organ scale. We therefore developed a diffraction-limited two-photon microscope that interleaves volumetric imaging with spatiotemporally focused line ablation, delivering a hundredfold increase in tissue removal efficiency and enabling fully optical in situ sectioning of the intact murine craniocerebral preparation. Custom control software fully automates acquisition by classifying osseous versus soft tissue on-the-fly, generating optimal tissue-dependent ablation trajectories, and continuously compensating for drift in the refractive index of the immersion medium, thereby keeping both imaging and cutting on target without human intervention. Peak ablation fluence and ablation translation speeds are carefully chosen to strike a balance between tissue-cutting precision and efficiency. As a demonstration of the microscope's capabilities, we then acquired a  $5.4 \times 4.2 \times 1.8 \text{ mm}^3$  craniocerebral data set captured at  $0.35 \times 0.35 \times 1.0 \text{ }\mu\text{m}^3$  voxel resolution during a multi-day unsupervised run. Our platform opens a path towards intact cerebrovascular atlases by enabling sectioning of mechanically heterogeneous craniocerebral preparations.



**Disclosures:** S. Huang: None. X. Ji: None. B. Friedman: None. D. Kleinfeld: None.

**Poster**

## **PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.11/WW6

**Topic:** J.02. Systems Biology and Bioinformatics

**Support:** NIH R01 NS116139  
NIH R56 MH132732

**Title:** Three-photon population imaging of subcortical brain regions.

**Authors:** \*H. FROSTIG<sup>1</sup>, A. MONASTERIO<sup>2</sup>, U. MISHRA<sup>1</sup>, J. GIBLIN<sup>1</sup>, J. C. MERTZ<sup>1</sup>, B. B. SCOTT<sup>3</sup>;

<sup>1</sup>Boston Univ., Boston, MA; <sup>2</sup>Psychological and Brain Sci., Boston Univ., Boston, UT;

<sup>3</sup>Psychological & Brain Sci., Boston Univ., Boston, MA

**Abstract:** Complex brain functions rely on the simultaneous processing of information across widespread brain regions, many situated deep beneath the cortex. Gaining insight into these processes requires monitoring neuroactivity from large cell populations in deep brain. Two-photon (2P) microscopy has revolutionized in vivo optical imaging, due to its ability to penetrate the brain of small animals despite optical scattering. However, while 2P microscopy can be used to perform calcium imaging in most of the mouse cortex, it lacks the penetration depth required to image subcortical structures. Three-photon (3P) microscopy is an emerging technology that provides superior depth penetration, due to reduced scattering of the excitation light and improved rejection of out-of-focus background. Previous demonstrations have successfully used 3P microscopy for non-invasive calcium imaging of the mouse hippocampus. However, the size of the fields of view (FOV) and the number of cells imaged using 3P calcium imaging have been limited, due to the high pulse energies required, increased tissue heating, and a decline in the signal-to-noise ratio (SNR) at greater imaging depths.

To address this challenge, we developed a Large Imaging Field of view Three-photon (LIFT) microscope, capable of recording neuroactivity from a 2 mm-diameter field of view at depths of > 1 mm in vivo. LIFT combines high numerical aperture (NA) optimized sampling, using a custom scanning module, with deep learning-based denoising, to enable population imaging in deep brain regions. We demonstrate non-invasive calcium imaging in the mouse brain from > 1500 cells across CA1, the surrounding white matter, and adjacent deep layers of the cortex, and show population imaging with high SNR in the rat cortex at a depth of 1.2 mm. The LIFT microscope allows for a flexible choice of imaging scale and rate and was built with all off-the-shelf components.

**Disclosures:** H. Frostig: None. A. Monasterio: None. U. Mishra: None. J. Giblin: None. J.C. Mertz: None. B.B. Scott: None.

**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.12/WW7

**Topic:** J.04. Physiological Methods

**Support:** RS-2024-00402116  
RS-2024-00335546

**Title:** Miniaturized microscope for real-time neural imaging in freely moving animals

**Authors:** \*H. JEONG<sup>1</sup>, Y. CHO<sup>3</sup>, S. JUN<sup>1,2</sup>;

<sup>1</sup>Dept. of Electronic and Electrical Engin., <sup>2</sup>Dept. of Brain and Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of; <sup>3</sup>Dept. of Med. and Mol. Genet., Indiana Univ. Sch. of Med., Indianapolis, IN

**Abstract:** The miniaturized fluorescence microscope (miniscope) has emerged as a transformative tool in systems neuroscience, enabling large-scale, cellular-resolution imaging of neural dynamics in freely behaving animals. Combined with genetically encoded calcium indicators such as GCaMP, miniscopes allow real-time monitoring of population-level neuronal activity, thereby facilitating investigations into the functional architecture of complex brain functions. These systems have been widely applied to studies of memory, reward learning, spatial navigation, and social behavior. Their compact, head-mounted design makes them particularly suitable for operant conditioning paradigms, maze-based tasks, and naturalistic behavioral assays. To further enhance functional imaging capabilities, dual-color fluorescence imaging allows the simultaneous observation of distinct neuronal populations or signaling pathways. However, previous implementations based on time-division multiplexing of excitation light sources have been constrained by limited temporal resolution and vulnerability to chromatic aberrations. In this study, we present a dual-color miniscope system that utilizes a color CMOS image sensor to directly acquire multicolor fluorescence signals without the need for sequential illumination or post-processing. Despite the inclusion of an achromatic lens in the miniscope, dual-color imaging requires chromatic aberration correction when using a monochrome CMOS sensor, whereas a color CMOS sensor enables more effective compensation. Additionally, depth information can be extracted by leveraging chromatic focal shifts. The optical and mechanical design builds upon the UCLA miniscope platform, ensuring compatibility with existing data acquisition hardware and software frameworks.

**Disclosures:** H. Jeong: None. Y. Cho: None. S. Jun: None.

**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.13/WW8

**Topic:** J.04. Physiological Methods

**Title:** Two-excitation wavelength (920 nm, 1064 nm) miniature two-photon microscope Mini2P for multicolor, freely behaving in vivo imaging

**Authors:** \*Y. WINTER;  
Humboldt Univ. - Inst. Biologie, Berlin, Germany

**Abstract:** Understanding how neural circuits function often means imaging the activity of multiple cell populations in behaving animals. Traditional head-mounted two-photon microscopes usually struggle to simultaneously excite and image different genetically encoded calcium indicators (GECIs) and other fluorescent reporters, especially those with far-shifted excitation spectra. We built upon the innovative Mini2P design and developed a Dual-Mini2P, a new head-mounted two-photon microscope that integrates two independent excitation fibers. This advancement enables true two-color imaging, utilizing distinct wavelengths of 920 nm and 1064 nm. The 920 nm channel works highly efficiently for exciting green indicators such as GCaMP. The 1064 nm channel effectively excites red fluorescent proteins such as tdTomato, and crucially, it allows us to directly excite and study the increasingly popular far-shifted GECIs. Furthermore, the Dual-Mini2P stays incredibly small, weighing about 3 grams, not significantly larger than the original Mini2P.

The Dual-Mini2P provides high-resolution, deep-tissue imaging in freely behaving mice. This lets researchers simultaneously investigate different neuronal populations or cellular processes labeled with spectrally separated indicators. This technological leap significantly broadens the types of experiments that can be performed for in vivo neuroscience, paving the way for new assays that demand monitoring multiple, molecularly defined neural elements during natural behaviors.

**Disclosures:** Y. Winter: None.

## **Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.14/WW9

**Topic:** J.04. Physiological Methods

**Support:** Horizon 2020 Framework Programme Project ID 101016787  
European Commission NextGenerationEU FAIR PE0000013  
Chan Zuckerberg Initiative Advancing Imaging Through Collaborative Projects 2023-2024

**Title:** Extended field-of-view two-photon functional imaging in the deep brain of freely moving mice

**Authors:** \*T. FELLIN, C. NARDIN, A. SATTIN, S. CURRELI, L. MADDALENA, G. LETTI; Optical Approaches to Brain Function Lab., Inst. Italiano di Tecnologia, Genova, Italy

**Abstract:** Miniaturized two-photon microscopes (MINI2Ps, [1]) enable high-resolution functional imaging in freely moving animals. To image deep regions of the mouse brain, MINI2Ps can be coupled to gradient index (GRIN) lenses. However, GRIN lenses suffer from intrinsic optical aberrations, which degrade the spatial resolution and decrease the size of the field-of-view (FOV). In this study, we tested the hypothesis that the optical performance of MINI2Ps coupled with GRIN lenses can be improved by using miniaturized aberration correcting optical elements [2,3] directly positioned on the back end of GRIN lenses (corrected GRIN lenses). When the MINI2P was coupled to corrected GRIN lenses, we found improved and more homogeneous spatial resolution across the whole FOV leading to an enlarged effective FOV compared to when the MINI2P was combined with uncorrected GRIN lenses. The enlargement of the FOV was confirmed by imaging subresolved fluorescent films and fixed brain slices. We then used MINI2Ps coupled to corrected GRIN lenses for longitudinal population imaging of jRCaMP7f-expressing neurons in the thalamic ventral posteromedial nucleus (VPM) of mice performing open field navigation. By sampling larger numbers of cells due to the extended FOV, MINI2Ps coupled to corrected GRIN lenses enabled the identification of sparse populations of thalamic neurons encoding behaviorally-relevant information. Taken together these results demonstrate that combining MINI2Ps with aberration corrected GRIN lenses is a powerful approach to enable large-scale high-resolution recordings of neuronal population activity in deep regions of the mouse brain during naturalistic behavior.

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- [2] A. Antonini<sup>†</sup>, A. Sattin<sup>†</sup>, M. Moroni, S. Bovetti, C. Moretti, F. Succol, ... and T. Fellin, *eLife* 9:e58882 (2020).
- [3] A. Sattin<sup>†</sup>, C. Nardin<sup>†</sup>, S. Daste, M. Moroni, I. Reddy, C. Liberale, ... and T. Fellin, *eLife* 13:RP101420 (2024).

**Disclosures:** T. Fellin: None. C. Nardin: None. A. Sattin: None. S. Curreli: None. L. Maddalena: None. G. Letti: None.

#### Poster

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.15/WW10

**Topic:** J.08. Methods to Modulate Neural Activity

**Support:** HOLOVIS-AdG” ERC2019-ADG-885090

**Title:** Precise two-photon all-optical manipulation of hippocampal circuits in unrestrained behaving mice

**Authors:** \*R. CASTILLO NEGRETE, D. DECOMBE, A. KUMAR, C. TOURAIN, V. DE SARS, N. ACANTO, V. EMILIANI;  
Sorbonne Université, INSERM, CNRS, Inst. de la Vision, Paris, France

**Abstract:** A central objective in neuroscience is to elucidate how neural activity gives rise to perception, cognition, and action, a pursuit that hinges on understanding the causal relationships between neuronal circuits and behavior (Marshall et al. 2019). The hippocampus, in particular, is essential for forming and consolidating episodic memory and plays a key role in spatial navigation by encoding and integrating environmental cues to support cognitive mapping (Ormond and O’Keefe 2022). The precise study of neuronal circuits requires the ability to measure and manipulate activity with high spatial and temporal resolution across large neuronal ensembles (Emiliani et al. 2022). All-optical approaches that combine two-photon (2P) calcium imaging with optogenetic photostimulation offer a powerful platform for in vivo circuit interrogation, though they have largely been confined to head-fixed animals (Emiliani et al. 2015). Despite these advances, studies demonstrating causal links between specific hippocampal neuronal circuits and behavior remain limited, largely due to technical challenges in achieving precise, cell-specific manipulation during complex, freely moving behaviors (Robinson et al. 2020). To overcome this limitation, we previously developed a flexible 2P holographic microendoscope, 2P FENDO, capable of all-optical circuits interrogation (Accanto et al. 2023, Blot et al. 2025). Here, by using gradient refractive index (GRIN) lenses in combination with micro-Tunable lens ( $\mu$ Tlens), we achieved 80 Hz functional Imaging and simultaneous multiplane photostimulation of individual and ensembles of CA1 pyramidal neurons within the hippocampal circuit of mice during spatial navigation and memory. By integrating behavioural tracking with closed-loop optogenetics, we enabled real-time manipulation of spatially tuned neurons in freely behaving mice. This approach establishes a powerful framework for uncovering how these neurons contribute to memory encoding during naturalistic behaviors. Our method offers a critical advancement for achieving precise, all-optical manipulation beyond the constraints of head-fixed paradigms.

**Disclosures:** R. Castillo Negrete: None. D. Decombe: None. A. Kumar: None. C. Tourain: None. V. de Sars: None. N. Acanto: None. V. Emiliani: None.

**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.16/WW11

**Topic:** J.04. Physiological Methods

**Support:** NIH Grant R01NS118289  
NIH Grant R21EB035306  
NSF CAREER 1847141  
Burroughs Wellcome Fund 1015761  
Burroughs Wellcome Fund 1019469  
NIH Grant DP2MH136588  
CIHR Award 202210MFE-491520-297096

**Title:** High-speed miniaturized two-photon microscopy in freely-moving mice

**Authors:** \*B. MATTISON<sup>1</sup>, Z. ZHANG<sup>1</sup>, S.-J. LIU<sup>1</sup>, J. MUIR<sup>1,2</sup>, N. SPURR<sup>1</sup>, C. K. KIM<sup>1,2</sup>, W. YANG<sup>1</sup>;

<sup>1</sup>Univ. of California Davis, Davis, CA; <sup>2</sup>Princeton Univ., Princeton, NJ

**Abstract:** Miniaturized two-photon microscopes (2P Miniscopes) are powerful optical tools that enable functional recording of neural activity at cellular resolution in freely-moving animals. 2P Miniscopes are generally limited in imaging speed as they build images pixel by pixel. Here, we present two different strategies to increase the imaging speed: beam multiplexing and point-spread-function (PSF) engineering. We developed two different beam multiplexing schemes, temporal multiplexing and computational multiplexing, which each increased the base imaging speed of the miniscope by  $\sim 2\times$  compared to the typical single point scanning designs. In PSF engineering, we reshaped the laser excitation into an elliptical spot at the sample, which reduces the number of raster scanning rows needed to build the image frame and thereby increases the imaging speed by  $>4\times$ . We built our miniscopes based on the MINI2P open source platform. Using our miniscopes, we performed *in vivo* volumetric calcium imaging in mouse visual cortex (V1) and medial prefrontal cortex (mPFC) through chronic cranial window and gradient index (GRIN) lens, respectively, while mice were free to behave in a  $40\times 28\text{ cm}^2$  open field. Volumetric refocusing capability was provided with an electrically tunable lens, and a constrained non-negative factorization (CNMF) method was used to extract neural footprints and activity. Mouse movement was recorded with an overhead camera and the mouse showed free behavior while wearing the miniscopes. We recorded neural activity during when the mouse was isolated or together with another mouse, as well as during an auditory stimulation protocol. We compared neural recordings of the same neurons between head-fixed and freely-moving conditions and found neurons that responded differently to auditory stimulation in each case. Additionally, with the increased speed of our miniscopes, we were able to record voltage indicator activity in freely-moving mice with a 400 Hz frame rate over a  $380\times 150\text{ }\mu\text{m}^2$  field-of-view (FOV). Our new miniaturized two-photon microscopes record neural activity over a large 3D brain volume at a high speed and will be important to study large-scale neuronal circuits during natural mouse behaviors.

**Disclosures:** B. Mattison: None. Z. Zhang: None. S. Liu: None. J. Muir: None. N. Spurr: None. C.K. Kim: None. W. Yang: None.

**Poster**

**PSTR251: Optical Methodology: Development: Optical Microscopy in Head Fixed and Freely Moving Mice**



**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR251.17/WW12

**Topic:** J.04. Physiological Methods

**Support:** CZI: 2024-338519  
NIH/NIDCD: 5R01DC020927

**Title:** Concurrent monitoring of neural activity and intracellular signaling in behaving animals with a miniscope-biosensor toolkit

**Authors:** \*S. GONZALEZ<sup>1</sup>, Q. DANIEL<sup>1</sup>, I. WONG<sup>1</sup>, M. KIM<sup>1</sup>, B. GRÄDEL<sup>2</sup>, J. TRUEB<sup>2</sup>, O. PERTZ<sup>2</sup>, K. A. BOLDING<sup>1</sup>;

<sup>1</sup>Monell Chem. Senses Ctr., Philadelphia, PA; <sup>2</sup>Inst. of Cell Biology, Univ. of Bern, Bern, Switzerland

**Abstract:** Dynamic intracellular molecular states shape neural function, but have primarily been studied in fixed tissue or in vitro. Lack of observations of these molecular influences in intact brains limits our understanding of processes controlling neural activity, plasticity, and memory. To address this, we developed a molecular and technological toolkit for imaging calcium and kinase activity sensors in single cells in vivo. Our imaging strategy combines ERK-KTR, a translocation-based fluorescent ERK activity reporter, with nuclear-localized GCaMP8m. GCaMP8m reports neural activity as a genetically encoded calcium indicator and enables the construction of nuclear masks to assess ERK-KTR sensor translocation between nucleus and cytosol. We generated a bicistronic construct co-expressing H2B-GCaMP8m and ERK-KTR-mScarlet and optimized expression conditions using AAV1 and AAV9 serotypes, parametrically varying vector dilution and volume via local and retroorbital delivery methods. Robust biosensor expression in hippocampal and neocortical cells is achieved within 4 weeks post-injection, revealing bright fluorescent signals both in vivo and post mortem. To facilitate accessible, low-cost signal acquisition in behaving animals, we developed a dual-color miniscope with achromatic optics, high spatial resolution (~4 µm/pixel, 19.6 MP sensor), and a modular assembly enabling easy sensor exchange (e.g., 5 MP sensor). The optics allow recording a 3 mm diameter circular area. We collected imaging data in fixed tissue and in vivo using the miniscope. Preliminary results confirm resolution is sufficient for computational imaging analysis and cell segmentation. Current efforts focus on optimizing imaging window preparations for long-term in vivo monitoring of ERK and calcium dynamics in hippocampal CA1 neurons. We present a toolkit merging molecular and systems neuroscience, enabling concurrent in vivo monitoring of intracellular signaling and neural activity with broadly-accessible imaging technology.

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**Poster**

**PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.01/WW13

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** R35GM150765  
R35GM134897  
R01MH113648  
U01MH136567)

**Title:** Uncovering mechanisms of orphan ligands identified by Endo-GeneScreen: a precision therapeutics approach

**Authors:** \*P. N. SAMOWITZ<sup>1</sup>, C. A. MILLER<sup>2</sup>, G. RUMBAUGH<sup>1</sup>;

<sup>1</sup>Dept. of Neurosci., The Wertheim UF Scripps Res. Inst., Jupiter, FL; <sup>2</sup>Mol. Med. and Neurosci., The Scripps Res. Inst., Jupiter, FL

**Abstract:** The Endo-GeneScreen (EGS) platform identifies small molecules that enhance the abundance of endogenous proteins from genes implicated in neurodevelopmental haploinsufficiency disorders (Michaelson, Samowitz et al., SFN Abstracts, 2025). For example, *SYNGAP1* Developmental and Encephalopathic Epilepsy (SYNGAP1-DEE) arises from reduced SynGAP protein in brain cells due to *de novo* loss-of-function SYNGAP1 variants. Previously, we reported that SR-1815 and numerous other orphan small molecules can double endogenous SynGAP protein abundance in *Syngap1* haploinsufficient neurons. These probes also mitigate significant cellular phenotypes of *Syngap1* deficiency, including synaptic and circuit hyperexcitability. However, since these probes were identified by phenotypic screening, their unknown mechanism-of-action (MOA) limits therapeutic development. Here, using SR-1815 as proof of principle, we demonstrate our emerging pipeline for elucidating MOAs of orphan ligands discovered via EGS. Initially, candidate molecular pathways were identified using a multilayered omics approach, including RNA-seq supplemented with proteomics, comparing wildtype and *Syngap1* mutant cortical neurons treated with vehicle or probe. Since SR-1815 robustly regulated transcription, causing corresponding protein-level changes, we employed MesoMap (Douglas, Samowitz et al., BioRxiv, 2025) to define chromatin mechanisms underlying its transcriptional effects. MesoMap revealed SR-1815 as a novel multi-kinase inhibitor controlling neuronal SynGAP abundance through multiple cellular processes. Specifically, SR-1815 inhibition of the CLK kinase family increased SynGAP protein levels by reducing inclusion of an alternatively spliced “poison” exon in *Syngap1* transcripts. Next, the full spectrum of SR-1815 kinase inhibition was determined via KinomeSCAN, revealing a profile resembling FDA-approved anticancer agents. Consistent with this, SR-1815 exhibited approximately 1000-fold selectivity for inhibiting proliferation in specific cancer versus standard cell lines, indicating potential for development into a broadly tolerated anticancer therapeutic. Collectively, these results underscore the essential need for MOA elucidation of orphan probes

from EGS. Currently, we are applying this deconvolution pipeline to additional probes identified for increasing SynGAP protein expression in neurons.

**Disclosures:** P.N. Samowitz: None. C.A. Miller: None. G. Rumbaugh: None.

## Poster

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.02/WW14

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** NIMH U01MH136567  
NIMH R01MH113648  
Praxis Precision Medicines UFAS-A00002

**Title:** The Endo-GeneScreen platform identifies drug-like probes that regulate endogenous protein levels within physiological contexts

**Authors:** \*S. MICHAELSON<sup>1</sup>, P. SAMOWITZ<sup>2</sup>, T. VAISSIÈRE<sup>2</sup>, C. ROJAS<sup>2</sup>, M. KILINC<sup>4</sup>, C. A. MILLER<sup>3</sup>, G. RUMBAUGH<sup>2</sup>;

<sup>1</sup>UF Scripps Biomed. Res., Jupiter, GA; <sup>3</sup>Mol. Med. and Neurosci., <sup>2</sup>The Wertheim UF Scripps Res. Inst., Jupiter, FL; <sup>4</sup>Grifols Therapeut., Research Triangle Park, NC

**Abstract:** Traditional phenotypic drug discovery platforms have suffered from poor scalability and a lack of mechanistic understanding of newly discovered phenotypic probes. To address this, we created *Endo-GeneScreen* (EGS), a high-throughput enabled screening platform that identifies bioactive small molecules capable of regulating endogenous protein expression encoded by any preselected target gene within a biologically appropriate context. We utilized genetic engineering to develop a Dual Luciferase Reporter (DLR) screening assay performed in primary cells from mice expressing two distinct luminescence-based reporters. The first luminescence signal is a readout of endogenous target protein abundance. The second luminescence signal reports global/non-specific changes in protein expression, as well as cellular toxicity in response to library compounds added to screening plates harboring primary cortical neurons. This assay system is high-throughput and was designed to screen large libraries of drug-like lead compounds. After screening >100,000 independent lead-like small molecules, *EGS* successfully identified more than a dozen distinct drug candidates capable of doubling endogenous SynGAP protein abundance within *Syngap1* haploinsufficient neurons. Because *Syngap1* haploinsufficiency causes a neurodevelopmental disorder, candidates that double SynGAP protein expression can be developed into pre-clinical precision drug candidates. As a proof-of-concept, we show how one compound, SR-1815, progressed through a rigorous validation pipeline. SR-1815 raised endogenous SynGAP protein in a variety of settings and also alleviated major cellular consequences of *Syngap1* loss-of-function. For example, in addition to

restoring normal SynGAP protein levels, this candidate also dampened synaptic and circuit hyperexcitability, a core manifestation of *Syngap1* haploinsufficiency in excitatory neurons. Furthermore, we demonstrate that *EGS* assays accelerate preclinical development of identified drug candidates and facilitate mode-of-action deconvolution studies (see related abstract - Samowitz, Michaelson *et al.*, SFN Abstracts, 2025). Thus, *EGS* identifies first-in-class bioactive small molecule probes, such as SR-1815, that promote precision drug development and biological discovery.

**Disclosures:** S. Michaelson: None. P. Samowitz: None. T. Vaissière: None. C. Rojas: None. M. Kilinc: None. C.A. Miller: None. G. Rumbaugh: None.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.03/WW15

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** NIH/NIDA Grant DP1DA058385  
Loma Linda University School of Pharmacy

**Title:** Novel Selective Dopamine D4 Receptor Ligands Differentially Improve ADHD-like Behaviors in the SHR/NCrl Rat Model

**Authors:** \*I. DELA PENA<sup>1,2</sup>, S. ANDINO<sup>2</sup>, A. AMIS<sup>2</sup>, M. ALKHATIB<sup>3</sup>, T. LI<sup>4</sup>, T. M. KECK<sup>3</sup>, C. A. BOATENG<sup>4</sup>;

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**Abstract:** Dopamine D4 receptors (D4Rs), part of the D2-like G protein-coupled receptor family, are highly expressed in the prefrontal cortex and limbic regions, and play key roles in cognition, attention, and reward. These features make D4Rs attractive targets for neuropsychiatric disorders such as substance use disorders, schizophrenia and attention-deficit/hyperactivity disorder (ADHD). However, therapeutic development has been hampered by the limited availability of selective and efficacious D4R ligands. The Boateng lab recently synthesized novel D4R-selective compounds, including FMJ-01-38 (high-efficacy partial agonist) and FMJ-01-54 (full antagonist). We investigated their behavioral effects in adolescent (4-6 weeks old) male spontaneously hypertensive rats (SHR/NCrl substrain), a validated model of ADHD, and Wistar rats as controls. Behavioral data were analyzed using two-way ANOVA to assess the influence of strain, dose, and their interaction. SHR/NCrls showed typical ADHD-like behaviors compared to Wistar rats, including hyperactivity (elevated locomotor activity in open field tests), inattention (reduced spontaneous alternation in the Y-maze), impulsivity (delay

discounting), and cognitive deficits (decreased novel object preference). FMJ-01-38 (5-10 mg/kg) dose-dependently reduced hyperactivity, improved attention and cognition, and decreased impulsive choice in SHR/NCrls. In Wistars, FMJ-01-38 also enhanced attention (10 mg/kg) and cognition (5 mg/kg). Conversely, FMJ-01-54 had no effect on hyperactivity but dose-dependently improved attention and cognition in SHR/NCrls, with no significant impact on Wistars. These findings show that both D4R ligands improve core ADHD-like behaviors in SHR/NCrls, with FMJ-01-38 also enhancing performance in Wistar rats. The differential behavioral outcomes may reflect distinct mechanisms of partial agonism versus antagonism at D4Rs, potentially involving divergent intracellular signaling pathways. Ongoing studies aim to elucidate these mechanisms and further define the therapeutic potential of these compounds.

**Disclosures:** I. dela Pena: None. S. Andino: None. A. Amis: None. M. Alkhatib: None. T. Li: None. T.M. Keck: None. C.A. Boateng: None.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.04/WW16

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** RIKEN Junior Research Associate Program  
Special Postdoctoral Researcher Program of RIKEN  
AMED under Grant Numbers JP22km0405214  
AMED under Grant Numbers JP24tm0524001  
AMED under Grant Numbers JP24wm0625001  
JSPS KAKENHI under Grant Numbers JP20H05777  
JSPS KAKENHI under Grant Numbers JP21H02855

**Title:** Systematic evaluation of effects and side effects of vafidemstat, a histone-modifying candidate therapeutic agent for psychiatric disorders, in a wildtype rodent model

**Authors:** \*A. KAWASAKI<sup>1,2,3</sup>, Y. NIWA<sup>1,4</sup>, H. SHOJI<sup>3</sup>, T. YOSHIHARA<sup>5</sup>, T. HARA<sup>1</sup>, T. MURANO<sup>3</sup>, K. HONDA<sup>1</sup>, M. ASANO<sup>5</sup>, T. TSUBOI<sup>4</sup>, T. KATO<sup>6</sup>, T. MIYAKAWA<sup>3</sup>, N. SASAKI<sup>2</sup>, T. NAKAMURA<sup>1</sup>, A. TAKATA<sup>1,4,6</sup>;

<sup>1</sup>RIKEN Ctr. for Brain Sci., Saitama, Japan; <sup>2</sup>Kitasato Univ., Aomori, Japan; <sup>3</sup>Fujita Hlth. Univ., Aichi, Japan; <sup>4</sup>The Univ. of Tokyo, Tokyo, Japan; <sup>5</sup>Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; <sup>6</sup>Juntendo Univ. Grad. Sch. of Med., Tokyo, Japan

**Abstract:** Large-scale genetic and genomics studies have shown that chromatin modification and transcription are critical in the molecular pathogenesis of neuropsychiatric disorders, such as autism spectrum disorder (ASD) and schizophrenia. In this context, inhibitors of lysine-specific histone demethylase 1 (LSD1) present promising avenues for new treatment strategies.

Supporting this, previous rodent studies showed that LSD1 inhibitors ameliorate disease-associated phenotypes in neuropsychiatric models by inducing broad transcriptome changes. Meanwhile, the widespread impact suggests that LSD1 inhibitors may have adverse side effects when administered to organisms in a non-pathological condition or genetically vulnerable subjects. To examine this, we investigated transcriptomic and behavioral changes in C57BL/6 wildtype mice treated with the brain-penetrant LSD1 inhibitor, vafidemstat. RNA-seq of the forebrain revealed 266 upregulated and 200 downregulated differentially expressed genes (DEGs), enriched for genetic risk factors of neuropsychiatric disorders. When we compared our DEGs with publicly available RNA-seq data from psychiatric patients and ASD and schizophrenia models, we unexpectedly found that DEGs in vafidemstat-treated WT mice showed significant enrichment in the same direction as those observed in ASD patients and in mouse models of ASD and schizophrenia, raising concerns about potential detrimental effects. However, when we analyzed overall DEG profiles in vafidemstat-treated and untreated WT mice and *Kmt2c* heterozygous knockout mutants, an ASD gene encoding histone methyltransferase, we found that both vafidemstat-treated mutant and WT mice show transcriptomic profiles intermediate between untreated WT and mutant mice. Therefore, vafidemstat may shift the transcriptome toward a specific state regardless of genotype. Behaviorally, vafidemstat-treated WT mice showed no major ASD- or schizophrenia-associated phenotypes, such as social or cognitive deficits, but exhibited reduced brain and body weights and diminished somatosensory responses. In summary, this study provides basic information on the transcriptomic and behavioral effects of vafidemstat, suggesting it stabilizes the transcriptome rather than inducing differential expression in one direction. Our results indicate that this compound produces minimal neuropsychiatric side effects, yet has the potential for physical and sensory side effects, highlighting not only the promise of vafidemstat as a therapeutic drug for neuropsychiatric disorders but also the necessity of careful monitoring when administering it to patients.

**Disclosures:** A. Kawasaki: None. Y. Niwa: None. H. Shoji: None. T. Yoshihara: None. T. Hara: None. T. Murano: None. K. Honda: None. M. Asano: None. T. Tsuboi: None. T. Kato: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sumitomo Dainippon Pharma. T. Miyakawa: None. N. Sasaki: None. T. Nakamura: None. A. Takata: None.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.06/XX1

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Title:** Modeling Trauma and Fear-Related Neurobehavioral Disorders in Zebrafish: A Translational Approach

**Authors: \*J. LEE;**

Biomed. and Pharmaceut. Sci., Idaho State University-Meridian, Meridian, ID

**Abstract:** Trauma- and fear-related disorders encompass a spectrum of anxiety pathologies characterized by dysregulated stress responses, altered fear learning, and persistent neurobehavioral deficits. Rodent models, though informative, present translational challenges for high-throughput screening and mechanistic dissection. Here, we explore zebrafish (*Danio rerio*) as a versatile model for trauma and fear-based anxiety research. Utilizing fear-conditioning paradigms, vulnerability/resilience stratification, and pharmacological interventions, we characterize behavioral phenotypes including freezing, altered locomotion, social withdrawals, and cognitive impairments. Neural circuit and molecular correlates are probed via ELSA and transcriptomic analyses, revealing conserved pathways of stress adaptation. These findings support the utility of zebrafish for dissecting the neurobiological underpinnings of trauma and fear disorders, and for accelerating discovery of novel interventions.

**Disclosures: J. Lee:** None.

## **Poster**

**PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.07/XX2

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** Digital In Vivo Alliance (DIVA)

**Title:** Long-duration digital home cage phenotyping greatly enhances reproducibility of behavioral studies

**Authors:** \*M. C. SAUL<sup>1</sup>, N. BRATCHER-PETERSEN<sup>2</sup>, M. RUIDIAZ<sup>3</sup>, J. OBERHAUSER<sup>3</sup>, S. BOLIN<sup>4</sup>, B. GASKILL<sup>5</sup>, T. L. ROBERTSON<sup>3</sup>;

<sup>1</sup>The Jackson Lab., Bar Harbor, ME; <sup>2</sup>Digital In Vivo Alliance / TLR Ventures, Redwood City, IL; <sup>3</sup>TLR Ventures, Redwood City, CA; <sup>4</sup>AbbVie, Lake County, IL; <sup>5</sup>Animal Welfare Integrity Assurance, Novartis Biomed. Res., Cambridge, MA

**Abstract:** Interlaboratory variation and noise challenge reproducibility, undermining confidence in preclinical behavioral neuroscience findings. Mastering the inherent variability in behavioral phenotypes holds significant scientific value, potentially improving reproducibility and translational success. New strategies are needed to understand and overcome rather than eliminate this variability. Using a novel digital home cage phenotyping system called Envision™ by JAX, we examined the interplay between individual variability; biological factors such as genotype and sex; and technical factors such as temporal replicate, study duration, and site. We adapted the study methodology from a classic study on interlaboratory variation but leveraged digital home cage measures as novel outcomes. We collected 21 days of digital home cage

activity data for both sexes of three different mouse genotypes (A/J, C57BL/6J, and J:ARC(S)) at three different sites over three different temporal replicates. We hypothesized that genotype would be the predominant biological contributor to phenotype, but with unknown contributions from technical factors and noise. The study documented 76,495 hours of digital home cage mouse life. The video data were processed using novel machine vision algorithms and cage-level activity was extracted from the datasets. The results indicate that variation strongly manifests at granular temporal resolutions. However, when analyzing the aggregated data, averaging over extended durations greatly increased the signal-to-noise ratio and allowed us to detect large genotype effect sizes. Further, we found that the signal-to-noise ratio varies by the circadian time of measurement. By combining long duration phenotyping of 10+ days with 24-hour data capture, the sample sizes needed for replicable results were greatly reduced as indicated by power analysis. These results demonstrate that long duration studies, where data are collected continuously in the home cage, can capture and overcome individual variation. The results also highlight how digital tools enable replication, enhance generalizability, and may ultimately improve translational outcomes in drug development. By integrating digital in vivo behavioral measures across domains such as neuromotor disease, epilepsy, and safety pharmacology, we can improve the fidelity of preclinical models to human conditions.

**Disclosures:** **M.C. Saul:** A. Employment/Salary (full or part-time): The Jackson Laboratory. **N. Bratcher-Petersen:** A. Employment/Salary (full or part-time): TLR Ventures. **M. Ruidiaz:** A. Employment/Salary (full or part-time): TLR Ventures. **J. Oberhauser:** A. Employment/Salary (full or part-time): TLR Ventures. **S. Bolin:** A. Employment/Salary (full or part-time): AbbVie. **B. Gaskill:** A. Employment/Salary (full or part-time): Novartis. **T.L. Robertson:** A. Employment/Salary (full or part-time): TLR Ventures. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TLR Ventures.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.08/XX3

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** I Want support from IBRO

**Title:** Fecal Microbiota Transplantation Ameliorates Quinpirole and Social Defeat Stress Generated Treatment Resistant Obsessive Compulsive Disorder in Rats

**Authors:** \***K. M. N. SHARMA, SRF**, M. DANDEKAR;  
Biol. Sci., NIPER HYDERABAD, Hyderabad, India



**Abstract:** Obsessive-compulsive disorder (OCD) is characterised by repetitive thoughts and behaviors. The gut microbiota dysbiosis has garnered attention in several brain disorders including the OCD. We speculated that the reshaping of microbiota-gut-brain axis may offer a novel therapeutic modality for managing OCD. In this study, we investigated the effect of fecal microbiota transplantation (FMT) in a treatment-resistant OCD (TRO) model of rats. TRO-like phenotypes were developed in rats by administration of quinpirole (0.5 mg/kg, intraperitoneal for 5 weeks) and social-defeat stress (SDS for 7 days). TRO-like behaviors in rats were assessed employing marble-burying test (MBT), self-grooming, hole board test (HBT), elevated-plus maze (EPM) and social-approach social avoidance (SASA) paradigms. The behavioral results indicated anxiety- and compulsive-like behaviors in rats exposed to quinpirole+SDS. Two-week FMT administration effectively reversed the TRO-like aberrations in rats. For instance, FMT-recipient animals showed decrease in number of marbles buried in MBT, lower self-grooming, less open arms exploration in EPM, more nose poking in HBT, and spent more time social chamber of SASA. The locomotor activity in open-field test and body weight remained unaffected across the groups. Post-behavioural assessments, blood, brain, intestine, and fecal samples were collected for q-PCR, NMR spectroscopy, and gut-histology studies. FMT significantly suppressed the elevated levels of mRNA/protein inflammasomes (NLRP3, ASC, caspase-1, and IL-1 $\beta$ ) in the frontal cortex of rats. Brain-derived neurotrophic factor levels remained unaffected across groups. The expression of tight junction proteins (ZO-1 and occludin) was restored in colons of FMT group. Additionally, FMT restored fecal and plasma levels of short-chain fatty acids and improved colonic villi/crypt ratios and goblet cell counts in TRO animals. These results suggest that FMT may rescinds quinpirole+SPS generated TRO-like phenotypes in rats by dampening inflammation in the brain and restoring intestinal functions.

**Disclosures:** K.M.N. Sharma: None. M. Dandekar: None.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.09/XX4

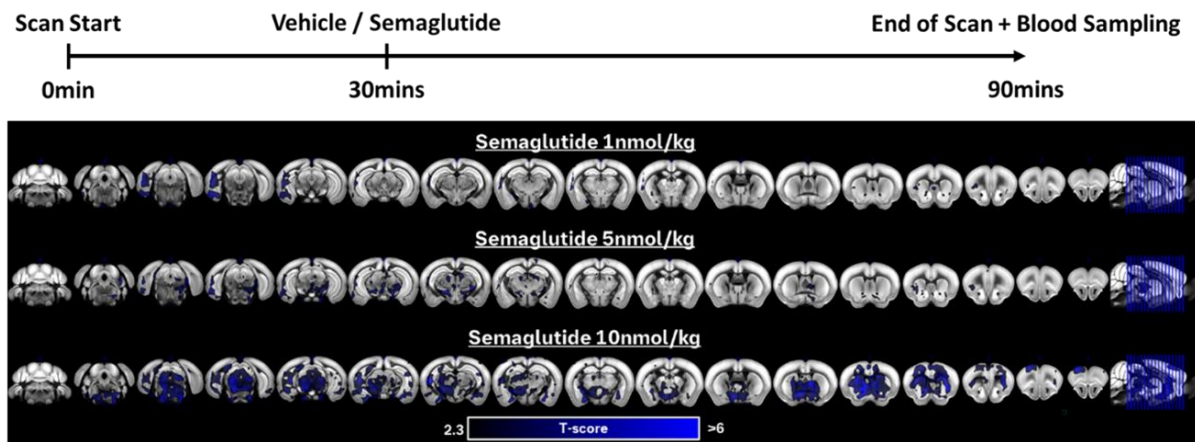
**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Title:** Semaglutide Induces Dose-Dependent Reductions in Cerebral Blood Volume and Functional Connectivity in Lean C57BL/6J Mice: A Functional Ultrasound Study

**Authors:** \*T. IONESCU<sup>1</sup>, V. MACK<sup>2</sup>, A. PEKCEC<sup>3</sup>;

<sup>1</sup>Dept. of Neurosci. and Mental Hlth. Discovery Res., Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; <sup>2</sup>Dept. of Cardio-Renal-Metabolics Discovery Res., Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach An Der Riss, Germany; <sup>3</sup>Dept. of Cardio-Renal-Metabolics Discovery Res., Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

**Abstract:** Semaglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, has emerged as a promising therapeutic for metabolic and, potentially, neuropsychiatric disorders, yet its central mechanisms remain incompletely understood. Here, we applied functional ultrasound (fUS) imaging to investigate dose-dependent effects of Semaglutide on brain-wide hemodynamics and connectivity. We scanned healthy, lean, 7-8 week-old male C57BL/6 mice under sedation (dexmedetomidine 0.09 mg/kg bolus + 0.06 mg/kg/h constant infusion + 0.5% isoflurane) using the Iconeus One (Iconeus, France) fUS scanner equipped with a multiarray probe covering the entire brain except the cerebellum. Animals received one of three doses (1nmol/kg, 5nmol/kg, 10nmol/kg) of Semaglutide or vehicle control intravenously, and fUS was used to assess changes in cerebral blood volume (CBV) and functional connectivity (FC) over 60 minutes following a baseline period of 30 minutes. The SPM12-based preprocessing pipeline included realignment, coregistration to Allen mouse brain atlas and spatial smoothing ( $0.3 \times 0.3 \times 0.3 \text{ mm}^3$  full-width-half-maximum). Additionally, filtering to 0.01-0.2Hz was applied for FC calculation. For CBV changes, the data were analyzed using the general linear model implemented in SPM12, while FC was assessed by computing Pearson's correlation coefficient between all pairs of regions and generating whole-brain correlation matrices. Semaglutide induced a robust, dose-dependent reduction in CBV compared to vehicle, most prominently in subcortical structures including the septum, substantia nigra, ventral tegmental area and interpeduncular nucleus ( $p < 0.01$ , One-Way ANOVA, Figure 1). Additionally, we saw a marked decrease in prelimbic and orbitofrontal FC ( $p < 0.01$ , ANCOVA), suggesting altered integrative processing in higher-order circuits. These findings demonstrate that Semaglutide exerts widespread neuromodulatory effects in the healthy brain, with implications for its cognitive and affective side-effect profiles and potential repurposing in neuropsychiatric contexts.



**Disclosures:** **T. Ionescu:** A. Employment/Salary (full or part-time): Department of Neuroscience & Mental Health Discovery Research, Boehringer Ingelheim Pharma GmbH & Co.KG, Biberach, 88397, Germany. **V. Mack:** A. Employment/Salary (full or part-time): Department of Cardio-Renal-Metabolics Discovery Research, Boehringer Ingelheim Pharma GmbH & Co.KG, Biberach, 88397, Germany. **A. Pekcec:** A. Employment/Salary (full or part-time): Department of Cardio-Renal-Metabolics Discovery Research, Boehringer Ingelheim Pharma GmbH & Co.KG, Biberach, 88397, Germany.

**Poster**

## **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.10/XX5

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** DARPA (HR00112320037)

**Title:** Correlation between TMS-evoked potentials (TEPs) and mental health outcomes

**Authors:** \*H. KIM<sup>1</sup>, J. KWEON<sup>2</sup>, P. GANESH<sup>2</sup>, G. VARONE<sup>1</sup>, K. J. RESSLER<sup>1</sup>, J. C. BROWN<sup>1</sup>;

<sup>1</sup>Div. of Depression and Anxiety Disorders, McLean Hosp. / Harvard Med. Sch., Belmont, MA;

<sup>2</sup>Div. of Depression and Anxiety Disorders, McLean Hosp., Belmont, MA

**Abstract:** Transcranial magnetic stimulation (TMS) combined with EEG offers a powerful approach for probing cortical excitability through TMS-evoked potentials (TEPs). Several recent studies have reported the potential of TEPs as diagnostic or predictive biomarkers in psychiatric disorders. However, the evidence is still limited and remains inconclusive. Given the early stage of research in this area, this exploratory study aimed to assess the potential relevance of TEPs to clinical outcomes. Ten participants with a diagnosis of depression, anxiety, or trauma-related disorders were randomly assigned in a double-blind manner to one of three groups: 1) D-cycloserine (DCS) + accelerated TMS (aTMS), 2) placebo + aTMS, or 3) placebo + sham TMS. Following drug administration (DCS 100 mg or placebo) in the morning of each experiment day, individuals underwent either aTMS or sham stimulation at the left dorsolateral prefrontal cortex (DLPFC). The stimulation sessions of 1800 pulses were repeated every hour, 10 times per day for three days. TEPs were measured before and after the first, second, and tenth stimulation sessions. At the beginning and end of each day, 200 TEP pulses were delivered. The remaining sessions were conducted with 150 pulses. The intensity for single-pulse TMS, used to measure TEPs, was 140% of resting motor threshold (rMT) electric field (V/m), and aTMS was 100% of rMT electric field. TEP data were preprocessed using toolboxes in MATLAB. After data preprocessing, P30, N45, P60, and N100 components at the left DLPFC were analyzed. In this study, multiple dimensions of mental health were assessed through clinical measures such as Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), Difficulties in Emotion Regulation Scale (DERS), and Big Five Inventory (BFI). Pearson correlation examined the relationship between TEPs and clinical measures. Although participants were assigned to different treatment conditions, the data were collectively analyzed using a bivariate correlation without separating groups, given the exploratory nature of the study and the limited sample size, which did not support reliable group-wise comparisons. To overcome this limitation, partial correlation was also performed. The analyses showed that TEP amplitudes collected immediately prior to the tenth treatment on Day 1 exhibited stronger correlations (most  $r_s > 0.8$ ) with changes in clinical outcomes from Day 1 to Day 5 than the other TEP values. These results suggest that TEPs may capture aspects of transient cortical homeostasis after aTMS

and may hold potential as predictive markers. However, further studies are needed to confirm these results.

**Disclosures:** H. Kim: None. J. Kweon: None. P. Ganesh: None. G. Varone: None. K.J. Ressler: None. J.C. Brown: None.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.11/XX6

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** Defense Advanced Research Projects Agency (HR00112320032)

**Title:** Network Reorganization in MDD patients Following rTMS: Evidence of Decoupling and its Association with Cognitive Flexibility

**Authors:** \*C. CHANG<sup>1</sup>, H. HE<sup>1</sup>, S. HASHEMPOUR<sup>4</sup>, G. DOYLE<sup>5</sup>, X. SUN<sup>2</sup>, J. DOOSE<sup>4</sup>, C. PING<sup>4</sup>, R. GONG<sup>4</sup>, L. HONG<sup>2</sup>, D. TAYLOR<sup>7</sup>, R. GOLDMAN<sup>8</sup>, M. S. GEORGE<sup>6</sup>, P. SAJDA<sup>3</sup>, L. MCTEAGUE<sup>4</sup>;

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**Abstract:** Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders worldwide. While rTMS (repetitive transcranial magnetic stimulation) has demonstrated clinical efficacy, the underlying neural mechanisms, particularly those related to cognitive flexibility, remain poorly understood. In this study, eight individuals with MDD underwent rTMS treatment. To assess changes in cognitive flexibility, participants completed a task adapted from Armbruster [1] both before and after treatment while undergoing functional MRI (fMRI). The task included three trial types, each targeting a specific cognitive state: ongoing trials measured non-interference, distractor trials evaluated cognitive stability, and switch trials tested cognitive flexibility. We analyzed beta correlations for each trial type to examine changes in functional connectivity post- and pre-treatment, focusing on both local and global brain networks. Specifically, we conducted two complementary analyses: (1) local network analysis examining post-pre connectivity differences between regions of interest, and (2) global brain network analysis using graph theory metrics, and how these metrics correlate with survey measures, such as the cognitive flexibility inventory (CFI). All participants showed reductions in HAM-D scores following treatment ( $t = 16.174$ ,  $p < 0.01$ ). The reported results focus on distractor trials, as these demonstrated significant effects. The local network analysis (Fig. 1) revealed consistent decoupling between the limbic and salience/ventral attention networks ( $-0.1334$ ,  $SE = 0.019$ ;  $p < 0.01$ ) and between the salience/ventral attention and default mode networks ( $-0.155$ ,  $SE = 0.028$ ;

$p < 0.05$ ), both surviving Bonferroni correction. At the global level (Fig. 2), changes in modularity negatively correlated with changes in CFI ( $r = -0.958$ ,  $p < 0.05$ ) after correcting for baseline CFI and baseline BDI scores, suggesting greater integration of brain networks may support improved cognitive function. These findings suggest that rTMS may drive clinical and cognitive improvements by decoupling salience networks and enhancing global integration, highlighting potential targets for personalized TMS protocols.

**Disclosures:** C. Chang: None. H. He: None. S. Hashempour: None. G. Doyle: None. X. Sun: None. J. Dooze: None. C. Ping: None. R. Gong: None. L. Hong: None. D. Taylor: None. R. Goldman: None. M.S. George: None. P. Sajda: None. L. McTeague: None.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.12/XX7

**Topic:** H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

**Title:** A whole-brain functional connectivity model to guide transcranial magnetic stimulation targeting for post-traumatic stress disorder

**Authors:** \*S. L. CHANDRASHEKAR<sup>1</sup>, H. GURA<sup>3</sup>, M. PATEL<sup>4</sup>, I. SUN<sup>1</sup>, D. F. GREGORY<sup>2</sup>, A. CASALVERA<sup>1</sup>, M. TEFERI<sup>1</sup>, N. L. BALDERSTON<sup>5</sup>;

<sup>2</sup>Psychiatry, <sup>1</sup>Univ. of Pennsylvania, Philadelphia, PA; <sup>3</sup>Univ. of Pennsylvania Neurosci. Grad. Group, Philadelphia, PA; <sup>4</sup>Univ. of Pennsylvania Dept. of Psychiatry, Philadelphia, PA;

<sup>5</sup>Psychiatry, Univ. of Pennsylvania Department of Psychiatry, Philadelphia, PA

**Abstract:** Post-Traumatic Stress Disorder (PTSD) is a debilitating psychiatric condition affecting approximately 3.9% of the global population. Although trauma-focused psychotherapy remains the first-line treatment, 14% to 35% of individuals fail to achieve symptom remission. Transcranial magnetic stimulation (TMS) has shown promise as an adjunctive intervention, but its efficacy for PTSD remains inconsistent, partly due to the lack of symptom-specific neuromodulation targets. This study aims to address that gap by identifying connectivity-based predictors of PTSD symptom severity to inform individualized TMS targeting. We developed a whole-brain atlas to predict TMS-induced changes in PTSD symptoms. We hypothesized that TMS reduces psychiatric symptoms by modulating the brain networks associated with those symptoms. This study used clinical (CAPS scores), structural (T1-weighted MRI), and functional (resting-state fMRI) data from a sample of 374 veterans with PTSD recruited from the Boston VA. Principal component analysis (PCA) was applied to functional connectivity matrices to reduce dimensionality, and the resulting component scores were entered into regression models to predict symptom severity. To simulate TMS effects, we generated electric field models for 200 randomly distributed coil positions across the cortex. We then generated a weighting matrix based on the vectorized, parcellated e-field distribution for each site to predict TMS-induced

changes in functional connectivity. Each site's parcellated, vectorized e-field distribution was used to create a weighting matrix, which was applied to the PCA regression coefficients to estimate TMS-induced symptom change. These values were then mapped back onto the cortex, and activation likelihood estimation was used to identify regions consistently associated with symptom improvement across individuals. This analysis revealed a distributed network of regions associated with significant reductions in PTSD symptoms, including areas in the posterior parietal cortex—suggesting that this parietal site may represent a promising novel treatment target for future studies. These findings support a data-driven framework for identifying symptom-relevant brain networks to inform precision-guided TMS. Ongoing work aims to map these features to anatomical targets and refine individualized stimulation strategies. By aligning brain network abnormalities with clinical symptoms, this approach has the potential to enhance the precision and efficacy of TMS treatment for PTSD.

**Disclosures:** S.L. Chandrashekar: None. H. Gura: None. M. Patel: None. I. Sun: None. D.F. Gregory: None. A. Casalvera: None. M. Teferi: None. N.L. Balderston: None.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.13/XX8

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** NIH grant R01MH129742 (Bipolar R01)

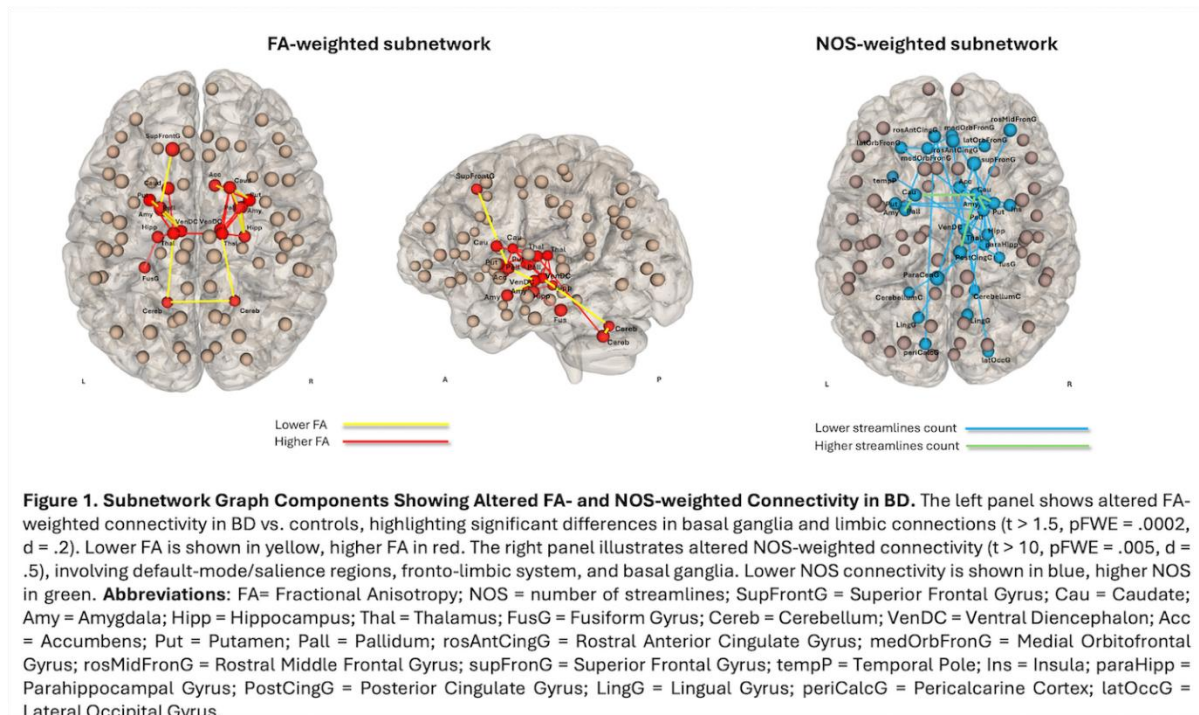
**Title:** Structural brain networks, polypharmacy and illness course in the ENIGMA Bipolar Disorder Working Group

**Authors:** \*L. NABULSI<sup>1</sup>, M. KANG<sup>1</sup>, N. JAHANSHAD<sup>1</sup>, P. M. THOMPSON<sup>1</sup>, O. A. ANDREASSEN<sup>2</sup>, C. CHING<sup>1</sup>, D. CANNON<sup>3</sup>;

<sup>1</sup>USC, Los Angeles, CA; <sup>2</sup>Ctr. for Precision Psychiatry, Inst. of Clin. Medicine, Univ. of Oslo, Oslo, Norway; <sup>3</sup>Clin. Neuroimaging Laboratory, Ctr. for Neuroimaging, Cognition & Genomics (NICOG), Galway Neurosci. Centre, Col. of Med. Nursing and Hlth. Sciences, Univ. of Galway, Galway, Ireland

**Abstract:** Bipolar disorder (BD) is associated with disruptions in brain networks supporting emotion regulation and reward processing. While structural MRI studies have identified brain abnormalities, detailed characterization of structural connectivity and the effect of psychotropic medications and symptom severity on these networks remains limited. This mega-analysis, the largest of its kind, leverages network analysis to examine associations between polypharmacy, illness course, and white matter (WM) connectivity in BD. We investigated structural brain networks in BD using diffusion-weighted MRI (dMRI), graph theory, and data from 449 individuals with BD (age: 35.7±12.6 y) and 510 healthy controls (33.3±12.6) across 16

international sites from the ENIGMA Bipolar Disorder Working Group. We used ENIGMA-standardized pipelines, non-tensor based tractography and subject nodal definition, to derive individual structural connectivity matrices and assess whole-brain and subnetwork-level architecture. Linear mixed models were used to examine associations with diagnosis, illness course, and medications—both conventional classes and classification based on mechanism of action—adjusting for age, sex, site, correcting for multiple comparisons. BD was associated with widespread WM disruptions, including lower network density and efficiency, longer paths, and higher centrality ( $d \approx 0.2$ ). Subnetwork changes were identified in emotion regulation, reward, and cognitive control circuits ( $d = 0.2-0.5$  Fig1). Illness duration, age of onset, and history of psychosis were associated with greater network disruptions. More lifetime manic episodes were associated with greater frontolimbic connectivity. Antidepressant, antipsychotic and anticonvulsant use were associated with poorer network architecture. These findings highlight robust, reproducible network-level alterations in BD and their relationships with lifetime symptoms and treatment, underscoring the value of large-scale efforts like ENIGMA in informing future network-based, personalized interventions.



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## Poster

### PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.14/XX9

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** R01MH078113-05  
R01MH103368-01  
R01MH077945-05  
R01MH077851-05  
R01MH103366-01

**Title:** Predictive Utility of White Matter and Bio-Factor Variables of Intrinsic EEG Activity in a Chronic Psychosis Sample (B-SNIP2)

**Authors:** \*A. BERARDI<sup>1</sup>, J. BROWN<sup>1</sup>, B. S. JACKSON<sup>2</sup>, L.-Y. HUANG<sup>3</sup>, R. TROTTI<sup>5</sup>, D. A. PARKER<sup>6</sup>, S. K. HILL<sup>7</sup>, E. I. IVLEVA<sup>8</sup>, G. D. PEARLSON<sup>9</sup>, C. A. TAMMINGA<sup>10</sup>, M. S. KESHAVAN<sup>11</sup>, S. KEEDY<sup>12</sup>, E. GERSHON<sup>13</sup>, B. A. CLEMENTZ<sup>4</sup>, J. E. MCDOWELL<sup>2</sup>; <sup>2</sup>Psychology, <sup>3</sup>Dept. of Psychology, <sup>4</sup>Departments of Psychology and Neurosci., <sup>1</sup>Univ. of Georgia, Athens, GA; <sup>5</sup>Beth Israel Deaconess Med. Ctr., Brookline, MA; <sup>6</sup>Genet., Emory, Atlanta, GA; <sup>7</sup>Rosalind Franklin Univ. of Med., Oak Park, IL; <sup>8</sup>Psychiatry, UT Southwestern Med. Center, Dept. of Psychiatry, Dallas, TX; <sup>9</sup>Johns Hopkins Hosp, Baltimore, MD; <sup>10</sup>UT Southwestern Med. Ctr., Dallas, TX; <sup>11</sup>Wayne State Univ., Detroit, MI; <sup>12</sup>Psychiatry and Behavioral Neurosci., <sup>13</sup>Univ. of Chicago, Chicago, IL

**Abstract:** Reduced white matter microstructure and elevated intrinsic neural activity have been observed in chronic psychosis samples. Further exploration of these relationships is needed by investigating potential predictive utility of white matter and electrophysiological features of functional neural activity. This study attempted to probe specific features of white matter microstructure and neurophysiological variables relevant to intrinsic neural activity in a chronic psychosis sample. 628 subjects were recruited through the multisite B-SNIP consortium with individuals diagnosed with schizophrenia, schizoaffective and bipolar disorder with psychosis probands and nonpsychiatric subjects. Diffusion-weighted images were acquired using 3T scanners, and mean FA values were calculated for 18 white matter tracts. Bio-factor data were collected, including cognition, saccadic eye movement data, and electroencephalography data. Results of a linear LASSO regression indicated coefficients of most relevance to intrinsic neural activity included: intrinsic activity-related biofactors on the paired stimulus and oddball tasks, ERP strength related biofactors, FA values for the left cingulum-parahippocampal portion, stimulus salience related biofactor, and RD values for the right inferior longitudinal fasciculus. Model performance was assessed with mean square error. At the optimal lambda, baseline MSE improved from 0.55 to 0.198. To validate our LASSO approach and reduce multicollinearity, we compared our results to Ridge regression. The LASSO and Ridge regression identified overlapping variables of interest: intrinsic activity-related bio-factors, ERP strength, latency bio-factor, P300 complex bio-factor and FA values for the left cingulum-cingulate gyrus portion. Model performance improved from 0.56 to 0.20 at optimal lambda. Both LASSO and Ridge regressions had a root mean square error (RMSE) of 0.042. Lasso R squared changes were 0.677 and Ridge regression were 0.681, indicating the Ridge regression model may capture more of the variance in intrinsic EEG activity compared to the LASSO model. These findings attempted to identify specific features of brain structure and neurophysiological variables and their relation to



functional neural activity in a chronic psychosis sample. These data may also enhance early detection of psychosis and biomarker stratification by utilizing a multimodal scientific approach.

**Disclosures:** **A. Berardi:** None. **J. Brown:** None. **B.S. Jackson:** None. **L. Huang:** None. **R. Trotti:** None. **D.A. Parker:** None. **S.K. Hill:** None. **E.I. Ivleva:** 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.; B-SNIP Diagnostics Board of Managers. F. Consulting Fees (e.g., advisory boards); Janssen Pharmaceuticals, Alkermes, Karuna Therapeutics. **G.D. Pearlson:** 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.; B-SNIP Diagnostics Board of Managers. **C.A. Tamminga:** 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.; B-SNIP Diagnostics Board of Managers. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Kynexis - retainer, Karuna - owns stock. F. Consulting Fees (e.g., advisory boards); Karuna, Kynexis. **M.S. Keshavan:** 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.; B-SNIP Diagnostics Board of Managers. F. Consulting Fees (e.g., advisory boards); Alkermes. **S. Keedy:** 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.; B-SNIP Diagnostics Board of Managers. **E. Gershon:** 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.; B-SNIP Diagnostics Board of Managers. F. Consulting Fees (e.g., advisory boards); Kynexis. **B.A. Clementz:** 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.; B-SNIP Diagnostics Board of Managers. F. Consulting Fees (e.g., advisory boards); Kynexis, Scientific Advisory Board. **J.E. McDowell:** 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.; B-SNIP Diagnostics Board of Managers.

## **Poster**

### **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.15/Web Only

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** RS-2023-00265883

**Title:** Regional radiomics similarity network analysis of brain structural alterations in patients with social anxiety disorder

**Authors:** \*D. LEE<sup>1</sup>, S. HONG<sup>4</sup>, M. KIM<sup>1</sup>, S. KWAK<sup>2</sup>, H. JI<sup>3</sup>, D. KANG<sup>5</sup>, S.-H. CHOI<sup>6</sup>;

<sup>1</sup>Dept. of Psychiatry, <sup>3</sup>Dept. of psychology, <sup>2</sup>Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of;

<sup>4</sup>Purdue University, West Lafayette, IN; <sup>5</sup>Psychiatry, Wonkwang Univ. Sanbon Hosp., Gunpo, Korea, Republic of; <sup>6</sup>Dept. of Psychiatry, Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

**Abstract:** Social anxiety disorder (SAD) is characterized by fear and/or avoidance of negative evaluation by others. Conventional group-level neuroimaging analyses have yielded mixed and inconclusive findings regarding structural brain abnormalities in SAD. Individualized approaches that leverage high-dimensional radiomics may offer greater sensitivity in detecting subtle deviations at the individual level. The present study employed a regional radiomics similarity network approach to quantify brain structural alterations and predict clinical severity in SAD. Radiomics were extracted from T1-weighted magnetic resonance images acquired from 67 patients and 78 healthy controls. Using the Brainnetome atlas, 22 radiomic features were extracted for each of 246 brain regions and normalized. Interregional similarity matrices were calculated for each subject by computing Pearson correlations between these vectors, resulting in individualized  $246 \times 246$  similarity networks. To assess deviations from normative patterns in each patient, we first constructed a reference network by computing the mean similarity matrix across healthy controls. Individual differential networks were constructed for each patient by adding the patient to the healthy controls to create a perturbed network and calculating the difference from the reference network. These differences were converted to Z-scores for brain region pairs, where negative values indicate reduced radiomics similarity relative to healthy controls (corrected  $p < 0.05$ ). Next, we identified the edges altered in  $\geq 5\%$  of patients ( $n$  of edges = 4,471), and used these as features in a random forest model with 5-fold cross-validation to predict individual clinical severity. The results showed that the differential edges in patients primarily connected frontal and temporal cortical regions with subcortical structures including the amygdala, thalamus, and basal ganglia. Functional annotation analysis of these edges revealed associations with cognitive terms such as perception, visual motion, face processing, and social interaction (permutation test,  $p < 0.05$ ). Predicted severity scores were correlated with actual scores in patients (Fear of Negative Evaluation:  $r = -0.534$ ,  $p < .0001$ ; Clinical Global Impression Severity of Illness:  $r = -0.424$ ,  $p = 0.001$ ), where patients with higher severity scores exhibited lower regional radiomics similarity. These findings demonstrate alterations in perceptual and social cognitive brain circuits critical for interpreting social cues and regulating affective responses in SAD, suggesting potential utility of individualized radiomics-based structural networks.

**Disclosures:** D. Lee: None. S. Hong: None. M. Kim: None. S. Kwak: None. H. Ji: None. D. Kang: None. S. Choi: None.

**Poster**

## **PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.16/XX10

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** VA CSR&D grant 1 I01 CX002182-01  
VA Office of Academic Affiliations, CA WRIISC Fellowship program

**Title:** The Role of Brainstem Imaging in Assisting the Diagnosis of Gulf War Illness

**Authors:** \*Y. ZHANG<sup>1</sup>, Y. RAHIMPOUR<sup>2,1</sup>, M. MOORE<sup>1,2</sup>, J. W. ASHFORD, Jr.<sup>2,1</sup>, P. J. BAYLEY<sup>1,2</sup>, A. J. FURST<sup>1,2</sup>;

<sup>1</sup>War Related Illness and Injury Study Ctr. (WRIISC), VA Palo Alto Hlth. Care Syst., Palo Alto, CA; <sup>2</sup>Stanford Univ., Palo Alto, CA

**Abstract:** Background: Gulf War Illness (GWI) is manifested by multiple chronic symptoms, including pain, sleep, neurological, gastrointestinal, respiratory, and skin problems in about 30% of Veterans who served in the 1990-91 Persian Gulf War (GW). We previously reported that Veterans with GWI showed selectively reduced brainstem volume compared to age-matched healthy civilians. The objective of this study is to test whether brainstem volume loss could be a key predictor of GWI in Veterans.

Methods: We recruited 59 Veterans, 39 who served in the Gulf War, and 20 who served in other combat or non-combat duties during the Gulf War Era. Participants' health was assessed for the presence and severity of GWI using CDC/Fukuda criteria. The severity of each symptom item was scored from 0 (none), 1 (mild), 2 (moderate), to 3 (severe). GWI severity was calculated from a total of 32 symptom items across 6 symptom domains. Based on these criteria, 23 Veterans were clinically diagnosed with GWI, while 36 Veterans were not (non-GWI). All Veterans underwent structural MRI scans. Volumes in regions of interest were measured using the FreeSurfer Atlas and Ascending Arousal Network (AAN) Atlas. Group differences and volume-symptom correlation were tested after regressing out confounders including age, sex, education, years in military, and total intracranial volume.

Results: There were no differences in symptom severity and brain volume between Gulf War Veterans and Gulf War Era Veterans. Compared to non-GWI Veterans, Veterans with GWI had substantially smaller volumes in the whole brainstem (5% smaller,  $p=.006$ ), brainstem segments including midbrain ( $p=.004$ ) and pons ( $p=.007$ ), brainstem nuclei including periaqueductal gray ( $p=.02$ ), locus coeruleus ( $p=.007$ ), dorsal ( $p=.004$ ) and medial ( $p=.002$ ) raphe nuclei. In the 39 Veterans who served in the Gulf War, greater GWI severity was associated with smaller volumes in the whole brainstem ( $\rho=-.50$ ,  $p=.001$ ), midbrain ( $\rho=-.43$ ,  $p=.007$ ), pons ( $\rho=-.53$ ,  $p<.001$ ), medulla, periaqueductal gray, nuclear accumbens, and cerebral cortex (each  $p=.02$ ).

Conclusion: Using a different data set of Veterans, this study replicated our previous finding that brainstem atrophy is a key feature of GWI. Volumetric analysis of the brainstem appears to provide critical insights into this chronic multi-symptom illness.

**Disclosures:** Y. Zhang: None. Y. Rahimpour: None. M. Moore: None. J.W. Ashford: None. P.J. Bayley: None. A.J. Furst: None.

**Poster**

**PSTR252: Translational Approaches and Experimental Therapeutics for Neuropsychiatric, Neurodevelopmental, and Neurological Disorders**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR252.17/XX11

**Topic:** J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Support:** Stanley Medical Research Institute grants 03-484 and 06T-797  
NIH NIMH/FIC/NCCAM grant R21MH095644  
NIH NIMH grant R21MH117776  
NIH NIMH/FIC/NCCAM grant R21TW011798  
Contract # HHSN-271- 2013-00017-C and HHSN- 271-2018-00023-C  
(NIMH - PDSP)

**Title:** Cxcr4 and cxcr7 (ackr3) as targets of cns-active phytopharmaceuticals

**Authors:** \*C. GALLO<sup>1</sup>, G. POLETTI<sup>1</sup>, B. CABANILLAS<sup>1</sup>, J. ALBAN<sup>2</sup>, C. MACHICADO<sup>1</sup>, K. F. VARA<sup>1</sup>, A. J. VAISBERG<sup>1</sup>;

<sup>1</sup>Univ. Cayetano Heredia, Lima, Peru; <sup>2</sup>Univ. Nacional Mayor de San Marcos, Lima, Peru

**Abstract:** The role of the chemokine GPCRs CXCR4 and CXCR7 (ACKR3) in the nervous system is still unclear. Although their natural ligands are known, much of their biology is far from being understood. It has been described that CXCR4 can form heterodimers with CXCR7, but also that they can signal independently. Interestingly, both receptors are highly expressed in several brain regions which are functionally linked: thalamus (paraventricular nucleus), hypothalamus (supraoptic nucleus), lateral ventricle choroid plexus, central glial substance, and medial habenula. There are also several brain regions on which both receptors express differentially. Noteworthy the brain regions expressing CXCR4 and CXCR7 are involved in reward processing but also in the regulation of pain. Rescuing traditional medicine practices is one of the possible avenues to discover novel pharmacological approaches. We have a repository of 477 extracts from an equal number of collections corresponding to 265 species from 87 different plant families used in Peruvian traditional medicine for treating brain disorders. We have identified 5 extracts with high activity for CXCR4 and 53 with high activity for CXCR7 (ACKR3) through a functional Tango-beta-arrestin assay performed at the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill. The active extracts are used in Peruvian traditional medicine for treating diverse behavioral conditions defined either in formal (depression, insomnia) and informal ("sadness", "madness", "aching heart", "nervousness") terminology. Our results so far show that many of the plants studied have a positive correlation in the activities for CXCR4 and CXCR7. This could support the presence of only one molecule activating both receptors at least in some extracts. The top 6

extracts are currently being fractionated and analyzed by LC-MS to isolate and characterize the active molecules. The isolated molecules will be pivotal not only to explore the potential of CXCR4 and CXCR7 as drug targets for mental disorders, but to advance in the understanding of the pathologic mechanisms involved in their occurrence.

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## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.01/XX12

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** NIH Grant R01 MH136198-01A1  
NIH Grant T32 MH019113-29A1

**Title:** Predicting stroke recovery with nonlinear low-dimensional embeddings of behavioral profiles

**Authors:** \*J. SKYE<sup>1</sup>, A. D. BOES<sup>2</sup>, D. KLIEMANN<sup>3</sup>, J. A. TRAER<sup>4</sup>;  
<sup>2</sup>Pediatrics, Neurol. & Psychiatry, <sup>1</sup>Univ. of Iowa, Iowa City, IA; <sup>3</sup>Univ. of Iowa, Iowa city, IA;  
<sup>4</sup>Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

**Abstract:** Stroke is a leading cause of disability, often impairing day-to-day functioning (e.g., mobility, socialization, independence in daily tasks). Predicting long-term functional outcomes remains challenging due to interindividual variability in both acute impairments and recovery trajectory. Prior studies have suggested that many post-stroke behavioral deficits are strongly correlated and can be summarized by low-dimensional latent factors. To date, it is not known whether such latent behavioral factors are predictive of chronic outcomes in stroke patients. Using data from 96 first-time unilateral stroke patients (45 female, mean age=53.8 ± 11.1 years) assessed acutely (7-14 days after stroke) and chronically (three months after stroke), we used 78 cognitive and motor metrics to predict 101 functional outcomes. We evaluated prediction accuracy of ridge regressions trained on full behavioral data versus those trained on latent factors (i.e., low-dimensional embeddings). Uniform Manifold Approximation and Projection (UMAP) embeddings (a nonlinear dimensionality reduction technique) preserved more predictive information than more standard linear embeddings (e.g., principal component analysis, factor analysis, etc.). Predictions derived from 2D or 4D UMAP embeddings were as accurate as those trained on the full (i.e., high-dimensional) dataset. To explore the structure in behavioral data captured by UMAP, we analyzed how behavioral profiles mapped into locations in UMAP embedding space. Multivariate lesion-symptom mapping revealed that patient proximity to specific extrema of the patient distribution (in the UMAP embedding) was associated with damage to bilateral subcortical structures, insular cortex, and adjacent white matter. Furthermore,

we identified four acute tests (bilateral Action Research Arm Test, left-hand 9-hole pegboard, and spatial span total score) whose linear combination best approximated the 4D UMAP embedding. Predictions derived from only these four tests matched the prediction accuracy of models using the full battery of predictors. These results highlight nonlinear low-dimensional embeddings of behavioral measures as powerful, interpretable tools for predicting chronic functional outcomes and mapping behavioral variation to lesion topography in stroke.

**Disclosures:** J. Skye: None. A.D. Boes: None. D. Kliemann: None. J.A. Traer: None.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.02/YY1

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** U01NS136507  
L.I.F.E. Foundation

**Title:** Topology-driven insights into naturalistic behavior from neuromechanical agent modeling

**Authors:** \*K. BIAN<sup>1,3</sup>, E. J. LEONARDIS<sup>1</sup>, Y. YANG<sup>1</sup>, C. ZHANG<sup>4</sup>, Y. WANG<sup>3</sup>, B. P. OLVECZKY<sup>4</sup>, T. D. PEREIRA<sup>2</sup>;

<sup>1</sup>Talmo Lab., <sup>2</sup>TPEREI, Salk Inst. for Biol. Studies, La Jolla, CA; <sup>3</sup>Halıcıoğlu Data Sci. Inst., UC San Diego, La Jolla, CA; <sup>4</sup>Harvard Univ., Cambridge, MA

**Abstract:** The brain doesn't exist in isolation; a vast amount of neurons in it serves the function of interacting with the world. New advances in realistic modeling of embodied agents in physics simulators have made it possible to study the brain in silico by mimicking a full agent-environment sensorimotor loop. These agents can be driven by neural controllers through the use of Deep Reinforcement Learning (DRL) enabled by parallelized GPU-accelerated physics engines such as MuJoCo-MJX to train an artificial agent with biomechanically realistic bodies by mimicking the behavior of real animals-the process is known as generative inverse kinematics and is supported by systems such as Mimic-MJX. Given the novelty of these new capabilities, few studies have explored the representations of natural behavior or its underlying neural computations that may be encoded in the neural controllers learned by artificial agents (e.g., weight matrices, intermediate activations). Existing studies of neural representations often leverage dimensionality reduction techniques that may distort the original shape of the data in favor of being able to visualize it in 2D or 3D. To address this challenge, we propose using Topological Data Analysis (TDA), to characterize high dimensional structure present in representations of embodied neuromechanical control. In this study, we utilized distance-to-measure-based persistent homology and density-based discrete Morse graphs to reveal interpretable signatures of behaviors. By applying these to a policy trained to control a virtual rat body, we discover patterns in the controller that reflect behaviorally-relevant motifs, such as gait

cycles and transitions between stereotypical behavior that were not readily identifiable in the full latent space. Such signatures provide the basis for new approaches to unsupervised behavior segmentation by exploiting how the neural network computations are grounded in the control task. Crucially, these methods are generalizable approaches for finding representations, agnostic to the body models or the task at hand. We hope this approach will provide the neuroscience community with new ways to interpret behaviors using topological invariants, in both naturalistic and artificial applications.

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## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.03/YY2

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** 2R01NS073717-06A1

**Title:** A Machine Learning Fall Prediction model for Parkinson's disease

**Authors:** E. A. JANSEN<sup>1</sup>, P. CANTLAY<sup>1</sup>, E. ZIMMERMAN<sup>2</sup>, A. ROSENFELDT<sup>1</sup>, C. LOPEZ-LENNON<sup>3</sup>, L. DIBBLE<sup>3</sup>, \*J. L. ALBERTS<sup>1,2</sup>;

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**Abstract:** Parkinson's disease (PD) is a progressive neurological disorder often associated with postural instability and gait dysfunction. A complex interplay of factors may increase fall risk in PD, with approximately 60% of patients falling annually and 39% transitioning into recurrent fallers as the disease advances. Despite the high prevalence of falls in PD, strategies to predict fall risk have seen little advancement; thus, identifying and intervening before fall conversion remains a significant challenge. The objective of this study was to determine whether retrospective analysis of participants who converted to fallers over a 12-month period could serve as a predictive tool for future PD cases. As part of a larger study, 246 Parkinson's disease patients were screened for participation and asked how many falls they experienced in the previous 6 months. Participants were given a falls diary with recording instructions and were telephoned biweekly by research personnel to confirm accurate fall(s) documentation. Of the 174 participants who reported no falls in the 6 months prior to enrollment, 94 reported no falls during the 12-month study, 47 reported exactly one fall, and 33 reported 2 or more falls. Due to the stochastic nature of falling, specifically in those without previous falls, those who fell exactly one time during the study can often provide the model with more noise than useful information. Therefore, those who fell exactly once were excluded from model training to reduce noise, allowing the model to focus on the strongest signal. An XGBoost model with repeated stratified

5-fold cross validation was trained and data from the 1-time fallers was added back for evaluation of model performance. The model achieved an average false positive rate of 0.39 and an average false negative rate of 0.46 across all folds. The large false negative rate was influenced primarily by the 1-time fallers, who had an individual false negative rate of 0.57 compared to the 2+ time fallers' false negative rate of 0.32. While prediction of isolated falls may be complicated by episodic factors, the model more effectively identifies patients with recurrent falls during the 12-month study. Explainable Artificial Intelligence was used to extract Shapley feature importance values for the seven variables comprising the model. Among the seven features were 2 self-reported quality of life measures, 2 cognitive assessments, and three technical balance assessments. Results provide rationale for the inclusion of quality of life measures and more sophisticated approaches to characterizing balance and postural stability in PD patients.

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## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.04/YY3

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** SMA Foundation

**Title:** Early Detection of ALS with Machine Learning-Based Behavioral Biomarkers in the SOD1<sup>G93A</sup> Mouse Model

**Authors:** \*O. BARKAI<sup>1</sup>, X. ZENG<sup>2</sup>, K. HEO<sup>2</sup>, N. MACKINNON-BOOTH<sup>2</sup>, C. J. WOOLF<sup>3</sup>; <sup>1</sup>Neurobio., <sup>2</sup>Boston Children's Hosp. and Harvard Med. Sch., Boston, MA; <sup>3</sup>Neurobio., Children's Hosp. Boston, Boston, MA

**Abstract:** Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease associated with progressive motor neuron degeneration and muscle paralysis. Current clinical diagnosis occurs only after significant neuronal loss, by which point neuroprotective therapeutic options are severely limited. To improve outcomes, early detection is critical—yet reliable, non-invasive biomarkers capable of identifying ALS prior to standard muscle weakness onset remain elusive. In this study, we present a machine learning (ML)-based framework to identify early, non-invasive behavioral biomarkers of ALS in the SOD1<sup>G93A</sup> mouse model. Using longitudinal pose estimation data collected over 16 weeks, we analyzed posture, movement dynamics, and body part kinematics in freely behaving mice. We hypothesized that early motor dysfunction—especially in passive behavioral states—could reveal disease-related changes before the standard clinical symptoms emerge. Our findings reveal that as early as 4 weeks of age, SOD1<sup>G93A</sup> mice exhibit subtle yet consistent alterations in postural stability and movement patterns, especially in



the cervical region. Using explanatory AI tools, we identified cervical muscle coordination as a key contributor to early ALS detection. We validated these results through behavioral assays targeting neck-related motor function. These assays demonstrated significant impairments in SOD1<sup>G93A</sup> mice compared to wild-type controls, reinforcing the notion that early cervical motor deficits may serve as accessible biomarkers of disease. Our approach demonstrates a robust detection of disease in SOD1<sup>G93A</sup> mice well before onset of standard motor function deficits, suggesting that early ALS-related neuromotor signatures can be detected using non-invasive, data-driven behavioral analyses. This work lays the foundation for translational biomarker development in high-risk human populations and may have applicability for other motor neurodegenerative disorders.

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## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.05/YY4

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** R01HD114776  
Research Accelerator Program of the Shirley Ryan AbilityLab

**Title:** A quantized autoencoder and language model-based approach for behavioral phenotyping

**Authors:** \*R. YANG<sup>1,2</sup>, A. KENNEDY<sup>3</sup>, R. COTTON<sup>2,1</sup>;

<sup>1</sup>Northwestern Univ., Chicago, IL; <sup>2</sup>Shirley Ryan Abilitylab, Chicago, IL; <sup>3</sup>The Scripps Res. Inst., La Jolla, CA

**Abstract:** Recent advances in markerless pose estimation have made it possible to collect large volumes of behavioral data from animals and humans, with the goal of unraveling principles of motor control or detecting subtle changes in movement associated with injury or disease. But processing and drawing scientific conclusions from these tracking data remains a challenging and idiosyncratic process. Several existing algorithms aim to segment pose tracking data into a vocabulary of discrete behavioral motifs that reflect short-timescale movements. However, variations in the dynamics of a particular action can lead to over-segmentation of behavior, complicating data interpretation. To address this, we propose a new method to extract interpretable latent representations of human or animal behavior, based on modified vector-quantized variational autoencoders (VQ-VAEs). By learning a discrete set of behavioral syllables alongside a continuous embedding for execution style, our method compresses high-dimensional motion trajectories into a structured representation that supports behavior phenotyping. These representations may then be used to identify, compare, and track patterns of movement across individuals and time. We develop and optimize this pipeline on human movement datasets

collected on structured functional tests from participants with and without movement impairments. We then extend the same framework to animal behavioral recordings, testing the capacity of our model to capture fundamental movement syllables and execution styles across species. We show that our VQ-VAE model can be used to quantify movement impairment, where the representation of behavior corresponds to ground truth measures. To explore the broader utility of our model, we employ a language model-based approach. Treating the latent representation produced by our VQ-VAE model as a tokenization of movement, we fine-tune a language model to process and interpret these tokens in response to natural-language queries about activity type, impairment severity, and quantitative performance metrics. We set a baseline by training XGBoost classifiers for each of the tasks on histograms of tokens. This multimodal model outperforms XGBoost classifiers, showing that the learned embeddings capture clinically and biologically meaningful features without feature-engineering for each new task. Taken together, these results show the usefulness of the VQ-VAE representation, which can provide sensitive measures of motor dysfunction in injury and disease.

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## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.06/YY5

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Developing a zebra finch song classifier based on a convolutional neural network

**Authors:** K. C. BIEN<sup>1</sup>, S. ASADOORIAN<sup>1</sup>, J. MENDEZ<sup>2</sup>, \*B. G. COOPER<sup>1</sup>;

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**Abstract:** Songbirds are a powerful animal model for studying the process of vocal production learning - an imitative behavior necessary for language acquisition. It is well established that humans and songbirds have analogous interconnected neural circuits that function to enable vocal learning. Songbirds produce a wide variety of vocalizations, including producing multiple call types and their learned song(s). However, song learning and production is the most extensively studied vocal behavior because of the parallels it shares with human speech and language. Zebra finches (*Taeniopygia guttata*) are a commonly studied songbird because of their adaptability to the laboratory environment. During a typical daily recording session, zebra finches sing and call generating several hundred data files per day with only ~10-15% containing song. Many approaches can be used to classify song, but most rely on experimenters identifying unique features of an individual bird to segment the song within the recordings. This is a time-consuming process. Here, we sought to develop open-source, Python-based software that rapidly classifies song and generalizes across zebra finches without the need for user input to identify the bird's song. To this end, we developed a convolutional neural network-based classifier using song features from five zebra finches to distinguish zebra finch song from other common noises

in the recording environment (e.g., calls, cage noise, background conspecific song). To determine how robustly the classifier performed, we tested the classifier on 5 novel zebra finches under social housing conditions (conspecific vocalizations in the background). Ground truth was based on experimenters visually classifying song from spectrograms. The unsupervised classifier reliably identified zebra finch song (Cohen's kappa = 0.687), even with conspecifics in the background. Due to rapid processing speed of the underlying convolutional neural network, our classifier can process thousands of files in under a minute. Next, we explored whether the classifier would generalize to birds recorded in a novel zebra finch colony. Without additional training, song was accurately detected. We are developing a classifier for use in real-time data acquisition to allow for automatic song classification from singing birds. The existing open-source, classification software will provide researchers with an easily accessible and useful tool for the first step in their data analysis pipeline - enabling rapid and efficient identification of song data from zebra finches thereby enhancing the speed of scientific discovery of neural mechanisms underlying vocal imitation.

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### **PSTR253: Computational Approaches in Behavior**

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**Program #/Poster #:** PSTR253.07/YY6

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** National Institute of Dental & Craniofacial Research of the National Institutes of Health, Award Number DE027414  
National Institutes of Health's National Center for Advancing Translational Sciences, grant UM1TR004405

**Title:** Optimizing individual pain suprathreshold determination for multisite testing

**Authors:** \*A. HAGSTROM<sup>1</sup>, S. DUFFY<sup>2</sup>, R. NUWAILATI<sup>3</sup>, L. HUFFMAN<sup>3</sup>, E. J. MOANA-FILHO<sup>4</sup>;

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**Abstract:** In psychophysical pain research, often an accurate and efficient pain suprathreshold determination test is needed. Previous literature described several methods, however those focused on heat stimulation on a single site on the skin. For protocols that require heat stimulation using a single heating device over two separate testing sites within a body region such as the face, it poses a challenge. To overcome this limitation, we developed and tested two algorithms to determine the heat stimulus temperature required to evoke moderate pain when presented over two separate sites within the face: 1. The limit algorithm presents a series of heat

stimuli (range: 40-49°C, 1°C steps) with adaptive branching logic that requires at least one rating from each tested site to be within a “moderate pain” range (30-69 in a 0-100 visual analogue scale (VAS)); 2. The regression algorithm initially presents two heat stimuli at preset temperatures (42°C, 47°C) to each test site. A linear regression model is calculated using four pain ratings (two temperatures x two test sites). The temperature predicted by the regression algorithm that elicits a pain rating of 50 and temperatures  $\pm 1^\circ\text{C}$  around it are tested (range: 40-49°C). To determine the temperature needed to evoke moderate pain, the regression algorithm requires a  $R^2 \geq .4$ , pain ratings truncated to 35-74 VAS, and a non-simulated temperature (i.e., tested on a participant) predicted by the final regression model to evoke a pre-determined pain rating (e.g., 50 VAS). Using the limit algorithm, 58 adult females including chronic jaw pain cases (n=34) and age-matched pain-free controls (n=24), were tested by applying heat stimuli (10s duration, ramp-up/down rate=1°C/s) on the left side of the forehead and chin using a 30x30mm thermode. Out of the 58 participants, 45 (78%) had an algorithmically determined temperature evoking moderate pain (mean 45.5°C), while 13 (22%) did not due to the algorithm’s limitations in accommodating pain ratings variability. To test the regression algorithm, 10,000 individuals were simulated as providing pain ratings at every step of the algorithm. Simulated temperatures and pain ratings were used for threshold (39.9°C  $\pm 3.7$ ; rating=0 VAS) and tolerance (45.9°C  $\pm 3.3$ ; rating=100 VAS). 9,133 of 10,000 (91%) simulated individuals had the temperature evoking moderate pain determined, 2.5°C lower on average than the limit method. The regression algorithm’s determination of lower moderate pain temperatures and higher success rate suggest that it may be safer and a more accurate method for multi-site pain suprathreshold determination using heat stimulation.

**Disclosures:** **A. Hagstrom:** A. Employment/Salary (full or part-time): University of Minnesota School of Dentistry. **S. Duffy:** A. Employment/Salary (full or part-time): University of Minnesota School of Dentistry. **R. Nuwailati:** A. Employment/Salary (full or part-time): University of Minnesota School of Dentistry. **L. Huffman:** A. Employment/Salary (full or part-time): University of Minnesota School of Dentistry. **E.J. Moana-Filho:** A. Employment/Salary (full or part-time): University of Minnesota School of Dentistry.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.08/YY7

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Neurally synchronized timing for 2D and 3D experiments with PsyForge

**Authors:** \***J. BRUSKA;**  
Bruska Technologies LLC, Santa Monica, CA

**Abstract:** Accurate timing is the linchpin of behavioral and neurophysiological studies. With the shift toward more naturalistic and realistic experiments, more complex tools are becoming

required for experiment development, such as modern game engines. However, modern game engines have a critical flaw: they are not designed for the precise timings required for psychology and neuroscience experiments. The timings for reactions to outside stimuli and logging can easily be up to 17ms off (for a 60fps system). This amount of variation can make certain experimental methodologies completely infeasible, such as phase-locking to a stimulus. We present PsyForge, an open-source (GPLv3) experiment programming library, built on top of the Unity game engine, that is designed to address this exact issue when forging 2D and 3D experiments. It implements a safe, multi-threaded, event loop architecture capable of sub-millisecond precision. Additionally, it has been upgraded with a new logging system that records the actual time that stimuli appear on screen. Similar to other experimental programming libraries, PsyForge includes common components such as configuration, text display, audio recording, language switching, and an EEG alignment system. Additionally, since it is built on top of the Unity game engine, it automatically includes integration with Unity's extensive documentation, community assets, and cross-platform compatibility. With PsyForge, researchers can harness the creative breadth of modern game engines without compromising the temporal precision that behavioral and neurophysiological studies require.

**Disclosures: J. Bruska:** None.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

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**Program #/Poster #:** PSTR253.09/YY8

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** NSF GRFP DGE-2241144  
Burroughs Wellcome Fund CASI

**Title:** Adaptive stimulation & response modeling of neural latent dynamics in real time

**Authors:** \*J. GOULD<sup>1</sup>, A. DRAELOS<sup>2</sup>;

<sup>1</sup>Neurosci. Grad. Program, <sup>2</sup>Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

**Abstract:** Neural latent dynamics are a widely used framework in neuroscience for modeling the time evolution of low-dimensional neural data. These models have been established for neural decoding: for example, to translate from latent neural activity to ongoing kinematics in a motor task. To understand how such latent variables causally encode behaviors, and to subsequently use these factors to modify external outputs, would require methods for stimulating neural dynamics during an experiment. Algorithms to drive neural dynamics remain limited, however, due to the need to continually track ongoing changes in neural activity, to account for variation in neural responses under stimulation, and to select useful stimulations to apply from an extensive set of possibilities.

We developed a real-time method for stimulation-response modeling in arbitrary latent spaces,

and an optimization framework for selecting high-dimensional stimulation patterns to drive low-dimensional dynamics. Our method combines streaming latent space construction, a stimulus-aware kernel regression model of perturbed dynamics, and projection maximization under feasibility constraints to determine stimuli that move dynamics along a desired vector. We demonstrated our approach on both simulated and real neural data (calcium fluorescence images, intracortical electrophysiological recordings). We evaluated our method using three latent space representations and three predictive models of dynamics in parallel, and additionally provide a real-time estimator to determine which representation is most predictive of ongoing neural dynamics at any timepoint. This allows for direct comparison between different latent spaces and the opportunity for adaptive selection of stimulations to best distinguish amongst neural subspace hypotheses. Our method for the first time provides an end-to-end framework for stimulation of neural latent dynamics in real time, offering a promising avenue for both better understanding the causal relationship between neural activity and evoked behaviors, and for future brain-machine interface applications.

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## **Poster**

### **PSTR253: Computational Approaches in Behavior**

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**Topic:** J.06. Computation, Modeling, and Simulation

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Searle Scholars Award  
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**Title:** Collective motion in *Danionella* emerges from discrete copying interactions

**Authors:** P. PURI<sup>1</sup>, G. MEYERHOF<sup>2</sup>, J. L. NAPOLI<sup>2</sup>, D. ZADA<sup>2</sup>, M. LOVETT-BARRON<sup>2</sup>,  
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<sup>1</sup>Physics, <sup>2</sup>Neurobio., UC San Diego, La Jolla, CA

**Abstract:** Animals exhibit a dazzling array of collective behaviors. Recent studies have characterized the neural representations of relevant behavioral variables in group contexts, such as conspecific location and motion. However, much less is known about the neural mechanisms mediating interactions between individuals, and the sensorimotor transformations responsible for complex group behavior. To understand what behavioral algorithms underlie emergent group behaviors, we studied collective motion ('schooling') of micro glassfish (*Danionella cerebrum*).

Danionella schooling emerges during the first 8 weeks post-fertilization, concurrently with the development of neural responses to socially-relevant visual stimuli. This raises the question whether rules governing Danionella movements are simple and ‘reflexive’ (e.g., avoid collisions) or more complex (e.g., follow a specific leader). Rules spanning this range would require markedly different neural circuits for sensorimotor processing. Here, we propose a stochastic model with individual head-direction diffusion and pairwise alignment interactions. By fitting model parameters to behavioral data at different ages, we demonstrate how distinct developmental stages of schooling behavior- no-schooling, aggregation, and cohesive postural alignment - emerge from a decrease in diffusion, and a dramatic increase in propensity to match swimming directions with neighbors. Furthermore, this simple model quantitatively accounts for intricate group dynamics: age-dependent distribution of group-sizes, probability of schools merging/splitting, and sorting of mixed-age groups. This suggests that complex Danionella group behavior does not require sophisticated computations involving individual fish identity and group composition. Finally, analysis of behavior at the level of an individual reveals that fish generate distinct types of swimming responses which are consistent with the model, and that are subtly modulated by social context. In summary, our study demonstrates how complex, age-dependent group behavior emerges from changes in pairwise interactions, and opens a door for future investigations into the neural implementation of discrete social interactions underlying collective behavior.

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## **Poster**

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**Program #/Poster #:** PSTR253.11/YY10

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** NIH Grant RM1NS128775

**Title:** Translating preclinical SCS experiments to a clinical setting through an experimental and computational modeling pipeline

**Authors:** \*A. M. PORRAS LAURA<sup>1</sup>, L. MATTHEWS<sup>2</sup>, J. A. BEAUCHAMP<sup>4</sup>, L. RUIZ PEREZ<sup>6</sup>, I. SMITH FLORES<sup>2</sup>, T. AKAND<sup>2</sup>, C. WARWICK<sup>7</sup>, K. BATES<sup>4</sup>, M. S. GOLD<sup>8</sup>, S. ROSS<sup>7</sup>, H. KOERBER<sup>9</sup>, D. J. WEBER<sup>5</sup>, S. F. LEMPKA<sup>3</sup>;

<sup>1</sup>Biomed. Engin., <sup>3</sup>Dept. of Biomed. Engin., <sup>2</sup>Univ. of Michigan, Ann Arbor, MI; <sup>5</sup>Mechanical Engin. and Neurosci. Inst., <sup>4</sup>Carnegie Mellon Univ., Pittsburgh, PA; <sup>6</sup>Univ. of Michigan - Ann Arbor, Ann Arbor, MI; <sup>8</sup>Neurobio., <sup>7</sup>Univ. of Pittsburgh, Pittsburgh, PA; <sup>9</sup>Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

**Abstract:** Spinal cord stimulation (SCS) is used for managing intractable chronic pain. To date, many preclinical SCS studies have investigated the analgesic mechanisms; however, there are gross anatomical differences across species, leading to improper scaling of stimulation parameters between preclinical and clinical conditions. Here, we utilized a combined experimental and computational modeling approach to extrapolate our preclinical experimental findings to clinical conditions and improve our understanding of the neuromodulatory effects of SCS. Experimentally, we delivered epidural SCS to the low thoracic spinal cord in Sprague Dawley rats and recorded evoked compound action potentials (ECAPs) rostral to the stimulation site. We recorded ECAPs for various pulse widths (50-300 $\mu$ s) and frequencies (2-10,000Hz). We then employed a hybrid computational modeling approach, constructing finite element method (FEM) models to calculate the extracellular potentials generated by SCS, which we then applied to multi-compartment axon models to simulate the resulting neural response. We utilized this approach in models that replicated our preclinical experiments and in a human-scale model to simulate clinical conditions. Our preclinical-scale computational model showed strong agreement between experimental and simulated ECAP recordings, validating its accuracy in predicting neural recruitment. Using our human-scale model, we quantified spinal cord electric field strengths at clinical stimulation amplitudes. We then applied our validated preclinical-scale model to identify preclinical stimulation amplitudes that would produce equivalent field strengths. This analysis revealed a 2% scaling ratio: 20  $\mu$ A in preclinical experiments replicates the electric field of 1mA in clinical settings. While our findings are specific to our experimental design, they suggest many prior studies stimulate above the levels used clinically. To enhance translational value and mechanistic insights into SCS for pain treatment, preclinical studies should prioritize stimulation settings that replicate clinical conditions. Systematic translation of stimulation parameters between preclinical and clinical scales will improve our understanding of SCS and accelerate optimized therapies for improved patient outcomes.

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## **Poster**

### **PSTR253: Computational Approaches in Behavior**

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**Topic:** J.06. Computation, Modeling, and Simulation

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**Title:** Automated Gait Assessment of Pain Using Deep Learning with Long Short-Term Memory Network

**Authors:** \*Q. CHEN<sup>1</sup>, R. E. RHOADES<sup>2</sup>, T. DEAKIN<sup>2</sup>, P. TANG<sup>2</sup>, Y. XU<sup>2</sup>;  
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**Abstract:** Rodents' behavior in response to external noxious stimuli can quantify pain levels during pain development and management. This approach is widely used in evaluating analgesics for their pain-alleviation efficacy in many preclinical animal studies. However, experimenter biases in various pain assessments have attracted increasing scrutiny as such biases are responsible, at least partially, for the failure of many analgesic candidates in human clinical trials. An objective pain assessment method is highly anticipated in the discovery and development of new analgesics, considering the heavy public health burden in treating millions of Americans with chronic pain. Here, a deep learning (DL)-assisted gait analysis is developed to recognize rodents' gait patterns under different pain conditions. A high-resolution touchscreen is used as an animal-machine interface to collect rodent gait trajectories with and without inflammatory pain induced by the complete Freund's adjuvant (CFA). Multiple 12-minute segments of gait trajectories were collected from both male and female mice (N = 12) before and up to three days after CFA injection. The collected datasets were preprocessed as sequential segments with general gait features and then used to train a neural network with a deep learning algorithm utilizing the Long Short-Term Memory (LSTM) network and the convolutional neural network (CNN) to differentiate pain levels at different time windows after CFA injection. The trained network can distinguish pain levels with close to or better than 90% accuracy in the CFA-induced inflammatory pain model. Since thresholding reflexes are not involved in the pain evaluation, experimenter bias is completely removed in this objective and automated pain assessment. This approach will enable high-throughput analgesic screening with large datasets and deliver a reliable DL-assisted platform for preclinical pain measurements and eventually clinical applications for the discovery and development of new analgesics. (The work was supported in part by grants from the NIH, R01NS122830, T32GM075770, and T32NS073548, and by a seed grant from the Department of Anesthesiology and Perioperative Medicine at the University of Pittsburgh).

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**Poster**

**PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.13/YY12

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Lesa -- real-time and pose-free animal behavior classification via spatiotemporal enhanced transformer

**Authors:** \*Y. TAN<sup>1</sup>, T.-H. KUO<sup>2</sup>, C.-C. LO<sup>3</sup>;

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**Abstract:** Accurate and automated animal behavior classification is essential for neuroscience research. However, most state-of-the-art methods rely on pose estimation, which is not only time-consuming and computationally intensive, but also introduces significant complexity to the analysis pipeline. As a result, current automated workflows often involve multiple steps, making large-scale and real-time analysis challenging. To address these limitations, we present LESA (Lightweight and Enhanced Self-Attention), a simple yet highly effective video-based framework that enables multi-behavior recognition directly from raw video frames, completely bypassing the need for pose estimation. Our solution is built upon a customized lightweight backbone. Unlike conventional transformer-based approaches, our method preserves spatiotemporal features after the backbone. While prior works often implement self-attention mechanisms either along the temporal dimension or the spatial dimension independently, our approach integrates both by employing a custom self-attention mechanism with relative positional encoding. This joint attention mechanism allows the model to simultaneously capture complex spatial structures within each frame and temporal dynamics across frames. We evaluate our method on the CalMS21 dataset [1], a benchmark for mouse social interactions. Our model achieved average precision (AP) scores of 81.75 for attack, 89.72 for investigation, 96.35 for mount, and 98.46 for other behaviors, with a macro-averaged AP of 91.57 (macro-averaged across four behaviors; each AP calculated per class and averaged). Our model surpasses human-level annotation and delivers inference speeds exceeding 90 frames per second (fps), demonstrating both superior accuracy and real-time performance, as well as substantial improvements in pipeline simplicity. By leveraging transfer learning, we also minimize the effort required for individual laboratories to adopt and apply this model. This pose-free framework offers an efficient solution for high-throughput animal behavior analysis. **Reference:** [1] Sun, Jennifer J., et al. "The multi-agent behavior dataset: Mouse dyadic social interactions." *Advances in Neural Information Processing Systems* 2021.DB1 (2021): 1.

**Disclosures:** Y. Tan: None. T. Kuo: None. C. Lo: None.

**Poster**

**PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.14/YY13

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** ZIA DC000064, Poling  
Azure: OT2OD032100

**Title:** Envisioning New Clinical Data Pathways and Efficient Migration to Enhance nHEAR, a High-Quality, Cloud-Based Analytic Platform for Audiovestibular Clinical Data

**Authors:** \*J. R. URIARTE-LOPEZ<sup>1,3</sup>, C. ZALEWSKI, Sr.<sup>1</sup>, T. OH<sup>2</sup>, V. KAMATH<sup>2</sup>, L. ALLEMANG<sup>1</sup>, C. BREWER<sup>1</sup>, J. CHISHOLM<sup>1</sup>, J. CHRISTENSEN<sup>1</sup>, T. WAFI<sup>1</sup>, J. SAGET<sup>1</sup>, S. SAMPONG<sup>1</sup>, G. POLING<sup>1</sup>;

<sup>1</sup>Auditory and Vestibular Clin. Res. Section (AVCRS), <sup>2</sup>Information Systems Mgmt. Br., Natl. Inst. on Deafness and Other Communication Disorder (NIDCD), Bethesda, MD; <sup>3</sup>Ctr. for Alzheimer's and Related Dementias (CARD), Natl. Inst. on Aging, Bethesda, MD

**Abstract:** Computational audiology can support the use of Artificial Intelligence (AI) in both basic science and clinical settings. To properly train these AI models, large repositories of high-quality data are needed. Patient health data are expensive, difficult to collect, bound by many state and federal privacy laws, and often constrained by a lack of common data elements (CDEs) that prevent an efficient coalescence of data into a single repository. To overcome these challenges, we established **nHEAR**, a cloud-based platform to support auditory and vestibular clinical data. The goal of this specific project is: 1) to define and describe nHEAR clinical data pathways and 2) showcase complications in the data pathways and potential solutions. This project includes clinical data collected by the Auditory and Vestibular Clinical Research Section (AVCRS) at the National Institutes of Health Clinical Center. Findable, Accessible, Interoperable, and Reusable (FAIR) ethical data principles are integrated into our clinical data pathways. The data contained in nHEAR meet FAIR standards and include a comprehensive array of audiovestibular results. All siloed AVCRS datasets approximate 5GB of audiovestibular data from approximately 9000 unique individuals, spanning over 600 unique diagnosis codes including a healthy control dataset. Data logic strategies were employed using both Python and SQL queries to identify anomalous data streams across siloed vestibular databases. Manual data entry errors and inconsistencies across three locally siloed vestibular databases were characterized and initial CDE demographic anomalies were reviewed to establish a uniformed approach. For example, missing or inconsistent medical record numbers were identified in 343 cases. Additionally, when benchmarking against standardized diagnosis codes, inconsistencies in diagnosis name for the same intended code was frequently identified such as, "Autoinflammatory Disease", "Auto-inflammatory disease", or "Autoinflammatory disorder". This presentation highlights the importance of enhancing quality assurance within data pathways when developing large, scalable clinical datasets. High-quality audiovestibular data is vital to the precision of nHEAR. Identifying data anomalies and correcting them will increase the accuracy of data during the migration and merge processes. This work improves our understanding of network processes, streamlines migration and merging efficiencies, and strengthens the accuracy of the nHEAR repository.

**Disclosures:** J.R. Uriarte-Lopez: A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). C. Zalewski: A.

Employment/Salary (full or part-time): University of Maryland, National Institute on Deafness and Other Communication Disorders. **T. Oh:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). **V. Kamath:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). **L. Allemang:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). **C. Brewer:** None. **J. Chisholm:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). **J. Christensen:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). **T. Wafa:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). **J. Saget:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). **S. Sampong:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD). **G. Poling:** A. Employment/Salary (full or part-time): National Institute on Deafness and Other Communication Disorder (NIDCD).

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.15/YY14

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Automated mild cognitive impairment detection (PD-MCIx) in patients with Parkinson's Disease

**Authors:** \***C. XIE**<sup>1</sup>, D. A. GITELMAN<sup>1</sup>, J. ADLER<sup>3</sup>, D. SCHIEHSER<sup>2</sup>;

<sup>2</sup>Dept. of Psychiatry, <sup>1</sup>UC San Diego, San Diego, CA; <sup>3</sup>VA San Diego Healthcare Syst., San Diego, CA

**Abstract:** Parkinson's disease-mild cognitive impairment (PD-MCI) is the diagnosis of mild cognitive impairment (MCI) within the context of Parkinson's Disease (PD). PD-MCI is associated with an elevated risk of further cognitive decline and progression to Parkinson's Disease Dementia (PDD). As PDD typically involves more substantial cognitive deficits and functional impairment that necessitate assisted living, research in PD-MCI has garnered much academic and industry interest. However, existing methods of PD-MCI diagnosis often rely on manual scoring, idiosyncratic algorithms, or complicated software; these approaches can be time-intensive, error-prone, or inaccessible due to high costs and limited customizability. Currently, no publicly-available tool exists to automate the diagnosis of PD-MCI based on objective cognitive, subjective cognitive, and functional impairment utilizing neuropsychological data. Therefore, we created PD-MCIx, an open-source diagnostic tool available for download in R and Python, and available via the Hugging Face platform (<https://github.com/conxie/PD-MCIx>). The tool employs rule-based logic derived from the 2012 Movement Disorder Society Task Force criteria for PD-MCI diagnosis and was validated with two independent datasets:

Dataset\_1 (n = 99) and Dataset\_2 (n = 181). Both datasets contained baseline scores (i.e., neuropsychological assessments and self report surveys) where the parent studies evaluated neuropsychological functioning in those with PD. Datasets contained licensed neuropsychologist (clinician)-reviewed diagnoses which were used as a benchmark to evaluate diagnostic accuracy of PD-MCIX. Two part validation was done using Cohen's Kappa and a proportion test. For both datasets, there was substantial agreement between the algorithm and the clinical diagnosis,  $\kappa = .64$ , 95% CI [0.49, 0.78] (Dataset\_1) and  $\kappa = .70$ , 95% CI [0.57, 0.83] (Dataset\_2), indicating that the automated classification aligned well with clinician reviewed diagnoses. The proportion tests revealed 81.9% (Dataset\_1) and 91.6% (Dataset\_2) accuracy with clinician-reviewed diagnosis based on participant data. Results indicate that PD-MCIX is comparable to clinician reviewed diagnoses, and thus, PD-MCIX is a valid tool that researchers can use to assist in the identification of PD-MCI.

**Disclosures:** C. Xie: None. D.A. Gitelman: None. J. Adler: None. D. Schiehser: None.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.16/YY15

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** NIH Grant R01DA044960

**Title:** Labgym: a new behavioral analysis software

**Authors:** \*E. L. SCHMIDT<sup>1,2</sup>, M. ELKOURI<sup>1</sup>, J. D. MORROW<sup>1</sup>;

<sup>1</sup>Psychiatry, Univ. of Michigan, Ann Arbor, MI; <sup>2</sup>Col. of Arts, Sciences, & Letters, Univ. of Michigan, Dearborn, MI

**Abstract:** Capturing the full scope and quantity of animal behavior is critical to neuroscience research, though our current tools still miss key details. Behavioral model organism assays require the observation and tracking of each animal in well-controlled and defined arenas, for increasingly extended periods of time. These experiments provide a wealth of information, often so detailed it is impractical to score manually. Current behavioral analysis software mostly relies on animal body posture, although this approach is not precise enough for many types of research questions and leads to discrepancies between human scoring and automated scoring. LabGym, an open-source computation tool, analyzes behaviors holistically using customizable neural networks. This software is suitable for experiments involving multiple animals, requires minimal programming knowledge to use, and provides visualization of behavioral datasets. Here, we demonstrate LabGym's efficacy in capturing subtle behavioral changes in male Sprague Dawley rats, as well as its ability to capture a novel fear expression in rats: scanning. We further compared LabGym's behavior scoring with manual scoring; LabGym successfully scored a range of behavior videos within a 95% confidence interval compared to human experts (n=4).

These results highlight LabGym's potential to enhance the accuracy and efficiency of behavioral scoring in neuroscience research.

**Disclosures:** E.L. Schmidt: None. M. Elkouri: None. J.D. Morrow: None.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.17/YY16

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** RS-2025-00521226

**Title:** Reconstruction of Postures Using Partial Body Information Through a Self-Supervised Transformer In Mice

**Authors:** \*C. KO<sup>1</sup>, D. KIM<sup>2</sup>;

<sup>2</sup>Biol. Sci., <sup>1</sup>KAIST, Daejeon, Korea, Republic of

**Abstract:** The comprehensive interpretation of behavior from incomplete data represents a fundamental challenge in computational ethology. Here we present Masked Autoencoder for Transformer-based Estimation and Reconstruction (MATER), a self-supervised learning framework that extracts behaviorally relevant representations from unlabeled rodent pose data by reconstructing strategically masked body keypoints. This approach captures fundamental movement patterns without requiring extensive manual annotation, addressing common experimental challenges including occlusions during social interactions and tracking errors. We evaluate MATER across two-dimensional and three-dimensional rodent pose datasets, demonstrating its robustness under high levels of keypoint masking. The framework achieves high-fidelity reconstructions under these challenging conditions and produces latent representations that support accurate behavioral classification with minimal supervision. Our analyses further reveal that rodent movement exhibits intrinsic spatiotemporal structure, which can be computationally inferred without explicit labeling. Reconstruction performance is tightly linked to the temporal coherence of movement, highlighting the importance of temporal dynamics in behavioral representation. These findings reinforce the emerging view that animal behavior is hierarchically organized and governed by natural temporal dependencies. MATER offers a robust, scalable tool for neuroscientists seeking to analyze complex, naturalistic behaviors across diverse experimental contexts, ultimately advancing our understanding of behavioral architecture and its neural underpinnings.

**Disclosures:** C. Ko: None. D. Kim: None.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.18/YY17

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** DOD PR221869

**Title:** Rest: a transformer-based model for automated mouse sleep stage classification

**Authors:** \*J. WANG<sup>1</sup>, M. V. JONES<sup>2</sup>, A. GOFORTH<sup>4</sup>, R. MAGANTI<sup>3</sup>;

<sup>2</sup>Dept Neurosci., <sup>3</sup>Neurol., <sup>1</sup>Univ. of Wisconsin Madison, Madison, WI; <sup>4</sup>Univ. of Wisconsin - Madison, Madison, WI

**Abstract: Background:** Sleep research in rodents often involves large-scale EEG/EMG recordings that are traditionally scored manually—a labor-intensive process prone to scorer bias and inconsistency. Although automated classifiers for rodents exist, most are based on Convolutional Neural Network or Recurrent Neural Network and struggle with limited temporal context, generalizability across strains, or require partial manual labeling. **Methods:** We developed REST, a Transformer-based neural network trained to classify mouse EEG/EMG epochs into Wake, NREM sleep, and REM sleep. EEG and EMG signals were segmented into 4-second epochs, transformed via short-time Fourier transform (STFT) to generate 2D representations with five-time frames and 130 frequency bins per epoch. Input sequences to the model were constructed as sliding windows of 90 consecutive epochs (6 minutes) with 30-epoch overlap. A dual-stage Transformer architecture was employed: the first stage encodes individual epochs with positional embedding and four Transformer layers; the second encodes the sequence of epochs using positional embedding and another four Transformer layers, preserving long-range temporal dependencies. The model was trained based on 180 days of artifact-free, pre-labeled EEG/EMG recordings from 94 FMR1 knockout mice (C57BL/6 background) and tested on seven 24-hour recordings from CD-1 mice subjected to traumatic brain injury (TBI). **Results:** REST achieved a Cohen's kappa of 0.867 and a classification accuracy of 0.93 compared to expert manual scoring, outperforming a comparable CNN-based model (Accusleep). REST showed high F1-scores for Wake (0.94) and NREM (0.92), with moderate performance for REM (0.82). Inter-scorer comparisons show that the level of disagreement between REST and human scorers is similar to the disagreement observed among human scorers themselves. REST was subsequently used to score over 3,000 days of EEG/EMG data from CD-1 mice in a TBI study where TBI and sham groups were treated with an FDA approved sleep aid, Lemborexant or vehicle. Analysis revealed that Lemborexant treatment significantly increased NREM and REM sleep during the 2-hour post-dosing period, thus validating REST's physiological relevance. **Conclusions:** REST is a fast, accurate, and consistent tool for automatic sleep staging in mice. Its Transformer architecture provides long-range temporal awareness and generalizes across mouse strains and models. REST enables scalable, unbiased, and reliable analysis of rodent sleep in large datasets.

**Disclosures:** J. Wang: None. M.V. Jones: None. A. Goforth: None. R. Maganti: None.

**Poster**

## **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.19/YY18

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** NIH R21  
NSF CRCNS US-Japan  
WU Tsai Human Performance Alliance at Stanford University

**Title:** Learning and Performance Trade-offs Across Tendon Stiffness Levels in a Simulated Robotic Limb

**Authors:** \***R. MIR**<sup>1</sup>, J. ZHANG<sup>1</sup>, F. J. VALERO-CUEVAS<sup>2</sup>;  
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**Abstract:** Passive elastic elements in tendon-driven limbs are integral to biological and robotic systems, contributing to their mechanical stability, energy efficiency, and shock absorption capabilities. However, such tendon-driven systems are simultaneously over- and under-determined, which poses specific challenges when developing autonomous learning algorithms for them. To systematically investigate these challenges, we employed a simulation-based reinforcement learning approach, which enables controlled experimentation and dynamic adaptation. In this study, we systematically evaluate the effect of tendon stiffness on the progression of learning using Proximal Policy Optimization (PPO), a reinforcement learning algorithm, when training a simulated tendon-driven leg walk. For each stiffness value, from 5 - 50 kN/m in 5 kN/m increments, we ran 10 independent learning trials. Each trial consisted of 1,000 episodes lasting 10 s. As a metric of performance, we recorded the distance walked (i.e., displacement) in each episode. Our results highlight that changes in tendon stiffness during training notably influence learning dynamics. We find that final displacement peaks at a stiffness value of 30 kN/m after which it drops sharply, indicating that very high stiffness can hinder effective movement. We further looked into the average rise time—the number of training episodes needed for the learning (displacement) to reach 70.7% of its peak—for each stiffness value. We found that rise time generally increased with stiffness, indicating that stiffer systems learn more slowly. These findings suggest a range of stiffness values that offer a favorable trade-off between learning speed and movement effectiveness, underscoring the importance of tuning compliance in tendon-driven robot design. This research underscores the significance of integrating adaptive learning processes with dynamically adjustable robotic components. These findings highlight how stiffness tuning and autonomous learning co-evolve in robotic systems, mirroring biological processes in which organisms adjust tendon elasticity to optimize locomotion. Such bio-inspired co-adaptation strategies could inform future designs of compliant, learning-enabled robots.

**Disclosures:** **R. Mir:** None. **J. Zhang:** None. **F.J. Valero-Cuevas:** None.

**Poster**



## **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.20/YY19

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Integrating Clinician Insights into Markerless Gait Analysis: Toward AI-Driven, Interpretable Gait Assessment.

**Authors:** \***L. REDDY**<sup>1</sup>, L. MCKAY<sup>2</sup>, B. ROGOZINSKI<sup>3</sup>, H. KWON<sup>4</sup>, T. M. KESAR<sup>5</sup>;  
<sup>1</sup>Dept. of Biomed. Informatics, Emory Univ., Atlanta, GA; <sup>2</sup>Emory Univ., Atlanta, GA; <sup>3</sup>Emory Univ., Grayson, GA; <sup>4</sup>Biomed. Informatics, <sup>5</sup>Physical Therapy, Emory Univ., Atlanta, GA

**Abstract:** Gait impairments are a prevalent, complex sequelae of aging, neurodegenerative processes, and neuro-pathologies, varying both within and across individuals. Traditional observational gait analysis relies on clinician experience, while marker-based motion capture, though precise, is costly and time-intensive. Recent advances in computer vision enable markerless gait analysis via video, but, existing approaches often require complex multi-camera setups and cloud-based processing, raising costs and privacy concerns. Moreover, Artificial Intelligence(AI) systems for gait classification lack the trust given to interpretable biomechanical metrics and human experience. We therefore (1) demonstrate feasibility of a smartphone-based markerless gait classification system and (2) Survey clinicians to adopt observational analysis metrics and evaluate their trust in AI. Videos were recorded for 27 able-bodied clinicians (4 men, 23 women; ages  $26 \pm 0.4$  and  $33.5 \pm 3.1$ ). Each performed one trial of seven simulated gaits (normal, circumduction, Trendelenburg, antalgic, crouch, Parkinsonian, vaulting). Two smartphones captured frontal and sagittal views, yielding 743 videos. Following standard human activity recognition methods our pipeline uses: BlazePose for on-device pose estimation, TSFRESH for time-series feature extraction, SMOTE augmentation, and classification using Support Vector Machine, Random Forest, and XGBoost. We used Leave-One-Subject-Out cross-validation and reported accuracy, F1, precision, and recall over ten trials with 95 percent binomial confidence intervals. Our survey of licensed clinicians collected demographics, clinical profiles, and gait analysis practices. Respondents labelled videos on gait type, severity, and movement-construct scores. XGBoost with combined views achieved the best F1 score:  $0.864 \pm 0.013$ . Sagittal F1 ( $0.794 \pm 0.014$ ) outperformed frontal ( $0.710 \pm 0.014$ ). Clinicians scored an F1-score of 0.882 on the same data. Inter-rater reliability in labelling gait classes was 0.84 but only 0.12 for severity and 0.18 for side affected. The classification pipeline matched clinician accuracy. Combined views outperformed single views by leveraging complementary information from asynchronous videos. Clinicians agreed on observed gait type but were inconsistent elsewhere. The model relied heavily on frequency (FFT coefficients), entropy, and joint directional trend features. Thus, AI can augment gait assessment with reproducible metrics when human judgment is variable. Future work focusing on ease of use, interpretability and privacy could enable broad rehabilitation adoption.

**Disclosures:** **L. Reddy:** A. Employment/Salary (full or part-time): Emory University. **H. Kwon:** None. **T.M. Kesar:** None.

**Poster**

**PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.21/YY20

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** RO1AG061785-AI

**Title:** Longitudinal and Age-Dependent Effects of Machine Learning on Spontaneous Behavior in Mouse Models

**Authors:** \*M. BULLOCK<sup>1</sup>, E. D. ROBERSON<sup>2</sup>, S. R. MILLER<sup>3</sup>, J. J. PALOP<sup>4</sup>;

<sup>1</sup>Univ. of Alabama at Birmingham (UAB), Birmingham, AL; <sup>2</sup>Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; <sup>3</sup>Gladstone Inst. of Neurolog. Dis., San Francisco, CA, ;

<sup>4</sup>Gladstone Inst. & UCSF, South San Francisco, CA.

**Abstract:** Traditional behavioral assays in mouse models often focus on domain-specific tasks (e.g., anxiety, motor function, memory) to evaluate experimental manipulations. While these methods remain critical, recent advances in machine learning (ML) enable unbiased, high-throughput analysis of spontaneous behaviors in naturalistic settings. ML techniques such as DeepLabCut and Keypoint-MoSeq automate pose tracking and behavioral sequence quantification, limiting human-defined behavioral categories that may not align with non-human models. However, the application of these approaches across longitudinal studies and diverse disease models remains largely underexplored. In this study, we systematically characterize the impact of repeated testing and aging on ML-driven behavioral analysis in C57BL/6 mice and neurodegenerative disease models. This work advances the utility of ML in translational research by addressing temporal and age-related confounds while validating its applicability across disease contexts.

**Disclosures:** M. Bullock: None. E.D. Roberson: None.

**Poster**

**PSTR253: Computational Approaches in Behavior**

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**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.22/YY21

**Topic:** J.06. Computation, Modeling, and Simulation

**Title:** Identifying motor representations that robustly generalize across subjects and behavioral contexts

**Authors:** \*F. H. TASCHBACH<sup>1</sup>, M. K. BENNA<sup>2</sup>;

<sup>1</sup>Neurobio., Univ. of California San Diego, San Diego, CA; <sup>2</sup>Neurobio., Univ. of California San Diego, La Jolla, CA

**Abstract:** Understanding neural representations across multiple subjects is challenging due to inter-individual variability in neural architecture and behavior execution. Current cross-subject analysis methods require temporal alignment or assume consistent anatomical relationships, limiting applicability to naturalistic behaviors. Previously we developed Shared Representation Discovery to identify common neural-behavioral relationships across individuals without temporal alignment. Here we examine whether these representations capture truly generalizable principles by testing their robustness across different behavioral contexts and neural systems. Applying this method to motor cortex recordings from three macaques performing center-out and random target reaching tasks, we found robust shared neural-kinematic relationships with cross-validated correlations  $>0.75$ . Remarkably, components trained on one task generalized effectively to the other task, with correlations remaining  $>0.6$  across animals, suggesting identification of conserved motor representations rather than task-specific patterns. Leave-one-animal-out validation demonstrated strong cross-individual generalization ( $r>0.6$ ), indicating that these representations capture shared computational strategies.

We demonstrate broader applicability with *C. elegans* whole-brain recordings during locomotion, showing robust cross-individual generalization. Applied to neuropixel recordings from mice across multiple brain regions, leave-one-region-out validation demonstrates that motor representations transfer between areas, suggesting distributed encoding of behavioral features throughout the nervous system. These analyses uncover conserved organizational principles across different neural systems. Comparison with existing methods shows that the framework maintains robust performance when temporal alignment assumptions are violated. These findings demonstrate that cross-subject analysis can identify conserved neural coding strategies that generalize across individuals, tasks, and brain regions.

**Disclosures:** F.H. Taschbach: None. M.K. Benna: None.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.23/YY22

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** DoD Vannevar Bush Faculty Fellowship  
Howard Hughes Medical Institute

**Title:** Extracting task-relevant preserved dynamics from contrastive aligned neural recordings

**Authors:** \*Y. JIANG<sup>1</sup>, K. SHENG<sup>1</sup>, Y. SHIKANO<sup>2</sup>, S. WOO<sup>3</sup>, F. DINC<sup>6</sup>, T. H. KIM<sup>4</sup>, S. LINDERMAN<sup>5</sup>, M. J. SCHNITZER<sup>7</sup>;

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**Abstract:** Recent work indicates that the low-dimensional dynamics of animal behavior and large-scale neural recording datasets may often be preserved across days and different subjects. However, the computational extraction of these preserved dynamics is commonly challenging, as the exact numbers and identities of cells in the set of neurons whose activity is recorded generally vary across recording sessions and animals. Although existing computational methods can facilitate alignments of neural activity and behavioral datasets, they often operate well only when applied to individual animals or recording sessions and may discretize behavioral parameters into categorical variables. These constraints may compromise descriptions of continuous behaviors and the identification of neural dynamical patterns that are shared across subjects. To address these challenges, we introduce Contrastive Aligned Neural Dynamics (CANDY), a computational framework that aligns neural and behavioral data with continuous variables using rank-based contrastive learning. CANDY projects high-dimensional patterns of neural activity from different recording sessions onto a shared low-dimensional embedding space, in which fits a shared low-dimensional linear dynamical system. To generalize across animals, CANDY projects neural activity from different brains onto a common space using a subject-specific encoder. It uses contrastive learning to align the latent embeddings, guided by the continuous behavioral data across sessions, such that the latent embeddings capture shared, behaviorally relevant factors. In parallel, CANDY learns latent dynamics with a linear dynamical system (LDS) to predict how the latent states evolve over time. This approach leads to an interpretable model with a conserved temporal structure in the latent space. We validated CANDY on several datasets acquired across different animal species, behavioral assays, and neural recording modalities. Our results show that CANDY identifies aligned latent embeddings and preserved dynamics across sessions and subjects, thereby achieving performance improvements in behavioral decoding when applied across multiple recording sessions. We further show that the latent linear dynamical system generalizes well to new sessions and subjects, yielding behavioral decoding performance values that can match or outperform models trained *de novo* on the additional datasets. These advances enable robust cross-session behavioral decoding and offer a path towards identifying common neural dynamical motifs that underlie animal behavior across individual brains and recording conditions.

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## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.24/ZZ1

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** European Fund for Regional Development

**Title:** Automated home cage monitoring and welfare assessment in laboratory rats

**Authors:** E. YILMAZ<sup>1</sup>, B. STOELLER<sup>3</sup>, W. VAN DOMMELEN<sup>4</sup>, A. SCHMAL<sup>5</sup>, J. R. HOMBERG<sup>2</sup>, \*L. P. J. J. NOLDUS<sup>6,4</sup>;

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**Abstract:** Background. Conventional laboratory rat housing restricts natural behaviors, disrupts circadian rhythms during daytime checks, and relies on labor-intensive, error-prone manual welfare checks. The ELAN (Efficient Lab Animal moNitoring) project addresses these issues by integrating automated sensors and machine learning into home cage systems for continuous behavioral and environmental monitoring in socially housed rats. Methods. The ELAN cage houses 2-4 rats and integrates a variety of sensors, including inertial sensors, ultrasonic microphones, and environmental sensors to monitor activity, vocalizations, food and water intake, temperature, humidity, and ammonia. Machine learning algorithms detect behavioral, physiological, and environmental deviations linked to stress or declining welfare at cage level. AI-driven analysis of frequency-specific ultrasonic vocalizations supports affective state assessment, while locomotor dynamics in enriched environments inform studies of motor function and neurodegeneration. The ELAN cage, electronics and software were benchmarked against an advanced automated cage system (PhenoTyper) and guided by requirements from workshops with academic, industrial, and regulatory stakeholders. Results. Based on our consultations, the ELAN system is expected to detect cage-level stereotypy, circadian disruption, scratching, and vocalization patterns. ELAN Pro modules will extend capabilities to individual animal analysis, including locomotor activity and affective state estimation. A cost analysis at a 500-cage facility predicts a 50% reduction in technician monitoring time, saving ~€180K/year, with return on investment in 2.5 years. Conclusion. ELAN has the potential to enhance behavioral monitoring through scalable, non-invasive technology, supporting both Refinement and Reduction in line with 3Rs principles. It can improve data validity, reduce variability, and lower operational burden, offering a cost-effective and ethical solution for preclinical research. Significance statement: The ELAN system offers a promising approach to improve animal welfare by enabling continuous, automated welfare assessment in group-housed rats using sensor integration and AI, improving data quality, reducing animal stress, and increasing translational relevance. Keywords: home cage monitoring, machine learning, ultrasonic vocalizations, rat behavior, animal welfare

**Disclosures:** E. Yilmaz: None. B. Stoeller: None. W. van Dommelen: None. A. Schmal: None. J.R. Homberg: None. L.P.J.J. Noldus: None.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.25/ZZ2

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** NIH U01NS136507  
L.I.F.E. Foundation

**Title:** Vnl-playground: fast and biologically realistic virtual environment for simulating animal behavior

**Authors:** \*Y. YANG<sup>1</sup>, E. J. LEONARDIS<sup>2</sup>, K. BIAN<sup>3</sup>, C. ZHANG<sup>5</sup>, E. AZIM<sup>6</sup>, B. OLVECZKY<sup>5</sup>, T. D. PEREIRA<sup>4</sup>;

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<sup>6</sup>MNL-E, Salk Inst., La Jolla, CA

**Abstract:** The brain evolved to move the body to interact with a dynamic world. To understand how it perceives, processes sensory input, generates action, and adapts behavior, we must study the full brain-body-environment loop. Advances in deep reinforcement learning (DRL) and fast physics engines like MuJoCo have enabled increasingly realistic in-silico simulations. However, these remain computationally expensive and often yield biologically implausible behaviors, limiting their usefulness for neuroscience. To address these challenges, we present VNL-Playground, a fast, GPU-accelerated software framework built on MuJoCo-MJX that enables efficient training of task-driven DRL agents in biomechanically realistic virtual bodies. Our platform is user-friendly and mirrors the design of MuJoCo Playground, while extending it with dynamic environment manipulation through `mj_spec`, allowing flexible task creation. Crucially, we support transfer learning through shared representations from Mimic-MJX (in preparation), a module that pre-trains virtual agents to produce biologically plausible motor behaviors by mimicking real animal motion. By grounding motor policies in both biomechanical realism and empirically observed behaviors, VNL-Playground helps bridge the gap between artificial and biological agents. This alignment enables more faithful comparisons between neural representations in simulated agents and those observed in animals, thereby enhancing the interpretability and biological fidelity of computational models. With VNL-Playground, we designed tasks like bowl escape and reach-to-target for virtual rodent models. Agents trained with transfer learning achieved higher rewards and displayed more naturalistic, biologically realistic movements. Training now completes within a day on a single consumer-grade GPU—previously a process that took weeks on large compute clusters.

By reducing the computational cost of virtual behavior modeling and emphasizing biological realism, VNL-Playground makes embodied neuromechanical simulation more accessible. Trained behavioral policies allow neuroscientists to study how the brain processes sensory input and generates decisions through bodily interaction with the environment. In preliminary experiments, we performed gait analysis alongside network activation profiling and found distinct activity patterns linked to different gait modes. This suggests our model's learned neural computations offer rich, behaviorally grounded representations. VNL-Playground is open-source and designed as an accessible tool for the neuroscience community.

**Disclosures:** Y. Yang: None. E.J. Leonardis: None. K. Bian: None. C. Zhang: None. E. Azim: None. B. Olveczky: None. T.D. Pereira: None.

## Poster

### PSTR253: Computational Approaches in Behavior

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.26/ZZ3

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** U01NS136507  
L.I.F.E. Foundation  
F32 NS126231  
Salk Pioneer Fund Postdoctoral Scholar Award

**Title:** Behavior-Driven Musculoskeletal Modeling for Embodied Neural Control: Dextrous Forelimb Reaching in Mice

**Authors:** \***E. J. LEONARDIS**<sup>1</sup>, Y. YANG<sup>2</sup>, A. NAGAMORI<sup>2</sup>, H. SAUNDERS<sup>2</sup>, A. BARBANO<sup>5</sup>, A. R. THANAWALLA<sup>3</sup>, K. BIAN<sup>2</sup>, E. AZIM<sup>6</sup>, T. D. PEREIRA<sup>4</sup>;  
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**Abstract:** We propose that understanding embodied control in the mammalian brain requires not only modeling neural circuits, but also capturing a full sensorimotor loop—from sensory input to musculoskeletal dynamics—so that behavior emerges from a tightly coupled brain-body system. We have developed a behavior-driven simulation for modeling high fidelity behavioral dynamics, biomechanics, and neural architectures underlying embodied control. A central question examined in this research is whether a behavior-driven reinforcement learning model constrained by motion capture data and biomechanics can predict muscular EMG recorded from the mouse during a forelimb reaching task. We present a mouse forelimb model in our Mimic-MJX and VNL-playground frameworks using muscle actuators to perform a dextrous reaching task based on an in vivo water reaching task. These frameworks benefit from a massively parallelized and optimized implementation in JAX, which exhibits a significant speedup over existing platforms. The biomechanics simulation was evaluated based on how faithfully it mimics kinematic and electromyography data observed in the lab, including joint trajectories, muscle force profiles, and timing of activation bursts. We also present results regarding the structure and generalizability of neural representations for embodied reaching. This work provides evidence to support the use of faithful biomechanics in embodied NeuroAI modeling, paving the way for improved interpretations of neural control strategies.

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## Poster

### PSTR253: Computational Approaches in Behavior

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.27/ZZ4

**Topic:** G.03. Stress and the Brain

**Title:** Entangled Knowledge, Uncertainty, Ambiguity, and Narrative Error Accounting in Bio-Psycho-Social Pain: A Quantum Mechanics-Inspired Approach to Episodic Experience and Authentic Self-Continuity

**Authors:** \*P. PENNEFATHER;  
gDial Inc, Toronto, ON, Canada

**Abstract:** *Proposition.* Chronic pain care journeys are structured by digital narrative schemas that encode Personal Health Record (PHR) data as future-oriented active inference processes. We present a framework integrating owned narrative representations of lived experience with self-authenticating PHR data to episodically colour care quality trajectory cognitive maps. This binds qualitative data→theory schemas (patient story knowledge) and quantitative theory→data practices (AI analytics based on data patterns), enabling Large Language Models (LLMs) to augment monitoring, evaluation, and guidance of pain care at system and meta-cognitive levels. gDial's patented system and methods facilitate co-creation/custody of paincare related knowledge within networks of individuals, communities, explicitly defined populations, and other entities with moral/ legal, and biophysical wants, needs, and rights, asserting privacy/autonomy while growing paincare LLMs as managed global public goods.

*Grounding.* Lived pain involves entangled uncertainty (explicit gaps) and ambiguity (tacit contradictions), forming narrative entropy where transitive (cause-effect) and commutative (context-dependent) aspects coexist. Drawing upon quantum error-correction analogies, we map Schumacher's knowledge fields: Inner-Self, Outer-Self, Outer-World and Inner-World (1st-4th person perspectives), as well as Franklin's concept of Holistic and Prescriptive technology, Nonaka's SECI model of knowledge growth, and Ahrent's human condition as attributes for segmenting personal narrative active inferences augmented via widely available ML/LLMs pipelines to support:.

1. *Encoding:* Anchor PHR data to vignettes capturing multi-perspective states (self-report, biometrics, social context)
2. *Detection:* Flag prediction errors via mismatches between LLM-generated narrative trajectories and observed outcomes
3. *Correction:* Recalibrate self-continuity authenticity perception.

*Justification.* By framing care journeys as mapable dynamic inference trajectories, the framework applies quantum-inspired "energy landscape flattening" to neuromodulatory gain modulation in chronic nociplastic pain in particular. This enables:

1. **Precision:** Differentiate maladaptive narrative rigidity (hyperfocus on threat) from adaptive uncertainty (exploratory model updating)



2. Agency: Patients co-steer LLMs to resolve ambiguity while preserving narrative coherence/authenticity
3. Scalability: Pooled, privacy-preserving story-data trains LLMs to predict care pathways that balance personalized needs with system-level resource allocation.

**Disclosures: P. Pennefather:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); gDial is a for-profit IP holding and licensing company wholly owned by the author and the family of one partner. All of the work presented has been self funded, PP is the sole surviving original owner of gDial and owns the IP together with the family of his deceased co-founder, West Suhanic.

## **Poster**

### **PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.28/ZZ5

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

**Title:** Routersense: a passive network-based monitoring system for early detection of adrd related behavioral changes

**Authors:** \***R. MAHMOOD**, D. HUANG;  
Electrical and Computer Engin., New York Univ., Brooklyn, NY

**Abstract:** Alzheimer's Disease and Related Dementias (ADRD) often manifest years before clinical onset through subtle behavioral changes—sleep disruption, fragmented routines, and digital disengagement. Yet current approaches to detecting these early signs—such as wearables, in-home sensors, and self-reports—are costly, intrusive, and prone to noncompliance. Traditional clinical assessments are episodic and miss day-to-day fluctuations, underscoring the need for a passive, scalable, and privacy-preserving solution for continuous behavioral monitoring. We introduce RouterSense, a plug-and-play system that repurposes commodity Wi-Fi routers into passive sensing platforms for digital behavioral phenotyping. Without accessing content or requiring app-level instrumentation, RouterSense analyzes encrypted network traffic data—such as flow timing, byte volume, and hostnames—to infer ADRD-relevant behavioral markers. In a two-week deployment (N=20), RouterSense passively identified behavioral markers linked to preclinical ADRD—such as delayed sleep-wake cycles, diurnal engagement patterns, and daily routine stability—using only encrypted network traffic. Figure 1 presents a time-aligned heatmap of one participant's device activity, revealing a late but consistent sleep routine: sustained low traffic from 04:00 to 11:00 (blue band) suggests a stable sleep-wake cycle with a delayed phase. This pattern was largely consistent throughout the data collection period, indicating temporal regularity rather than disruption. Hostname-level analysis revealed distinct patterns of app engagement, with social media platforms most active at night and productivity tools peaking in the late morning. These insights—extracted passively from encrypted network traffic alone—

demonstrate RouterSense's potential to detect early digital biomarkers associated with ADRD. Our results highlight a low-cost, privacy-preserving approach for continuous behavioral monitoring in naturalistic, unsupervised settings.

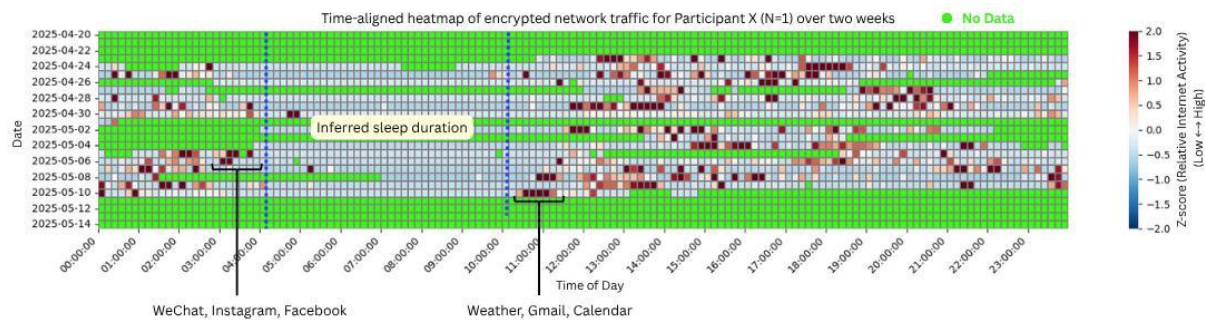


Figure 1: Sustained low traffic from 04:00–11:00 (blue band) indicates regular sleep timing. High nighttime app use (e.g., WeChat) and consistent morning activity (e.g., Gmail) suggest a stable diurnal routine.

**Disclosures:** R. Mahmood: None. D. Huang: None.

**Poster**

**PSTR253: Computational Approaches in Behavior**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR253.29/ZZ6

**Topic:** J.06. Computation, Modeling, and Simulation

**Support:** K08MH134028

**Title:** Functional Encoding Units represent interpretable attractor-like dynamics in neural ensembles

**Authors:** \*C. S. K. AKAFIA<sup>1</sup>, A. LIN<sup>3</sup>, D. E. BA<sup>4</sup>, N. JAIN<sup>5</sup>, A. ALLSOP<sup>2</sup>;

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**Abstract:** An important goal in neuroscience is to understand how the activity of individual neurons contributes to the broader networks that process stimuli and influence behavior. Clustering analysis can show partitions in high-dimensional neural recordings, revealing how groups of neurons co-activate during specific tasks. Attractor dynamics have been posited to underlie the neural activity that drives different behavioral states. Understanding these attractor dynamics in large-scale recordings is critical for linking single-cell activity to network function and behavior in animal models. However, most analysis pipelines either characterize only whole population or isolated neurons, rely on parametric assumptions, project data into an uninterpretable latent space or take a black-box approach. We introduce Functional Encoding Units (FEU) a state-space, non-parametric framework that clusters large populations of neurons

into ensembles located in an interpretable two-dimensional “jump-phasicity” space. Jump captures strength of neural response to stimulus and Phasicity captures its temporal persistence. This embedding reveals attractor-like states that govern population activity across varied experiments. On synthetic data, FEU surpasses K-Means, TSNE+K-Means, PCA+K-Means and CEBRA + K-Means in clustering accuracy. Applied to the Steinmetz et al. 2019 dataset, we find significant differences between encoding parameters as animals learn or change behavior in a visual-motor task. FEU reveals distinct attractor dynamics underlying choice representation by CA1 neurons compared to stimulus representation by VISp neurons characterized by an enhanced stimulus choice representation by CA1 and enhanced visual stimulus representation by VISp. Additionally, FEU shows distinct clustering dynamics in rodent and primate recordings consistent with attractor dynamics. In mice observing attack behaviors (Vinograd et al 2024), FEU shows significant change in representation of point attractor dynamics during attack compared to baseline. This shift in attractor representation is further validated in synthetic data that follow and do not follow attractor-like dynamics. FEU provides a pipeline for representing attractor-like dynamics and ensembles in an interpretable latent space across diverse animal models and experiments without making any prior assumptions about the structure of the data. This allows for decoding the computational primitives neural ensembles use to represent information and how those representations change as behavior evolves. FEU GUI is available at [feuccluster.com](http://feuccluster.com).

**Disclosures:** C.S.K. Akafia: None. A. Lin: None. D.E. Ba: None. N. Jain: None. A. Allsop: Other; Mefreely, LLC co-founder.

## Poster

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR254.01/ZZ7

**Topic:** J.04. Physiological Methods

**Support:** NIH Grant 4DP2MH129986  
JSPS KAKENHI Grant Number 23K28068  
JST ACT-X Grant Number JPMJAX190F

**Title:** Fully wireless, open-source Miniscopes for long-term neural recording in freely behaving animals

**Authors:** \*T. SASATANI<sup>1,5</sup>, M. BROSCHE<sup>1</sup>, F. SANGIULIANO JIMKA<sup>1</sup>, Z. DONG<sup>1</sup>, J. SAUNDERS<sup>1</sup>, H. SEMWAL<sup>2</sup>, P. ZHAO<sup>1</sup>, M. SEHGAL<sup>3,6</sup>, L. OESCH<sup>3</sup>, A. GUHA<sup>4</sup>, H. CHORST<sup>4</sup>, K. KEUS<sup>1</sup>, B. A. MADRUGA<sup>1,7</sup>, A. K. CHURCHLAND<sup>3</sup>, P. GOLSHANI<sup>1</sup>, D. AHARONI<sup>1</sup>;

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The Univ. of Tokyo, Tokyo, Japan; <sup>6</sup>Dept. of Psychology, Ohio State Univ., Columbus, OH;  
<sup>7</sup>Picower Inst. for Learning and Memory, MIT, Cambridge, MA

**Abstract:** Investigating the relationship between complex behavior and neural activity is a well-established approach in systems neuroscience. Miniature head-mounted fluorescent microscopes (Miniscopes) have enabled in vivo recording of neural activity in freely moving animals, greatly expanding the range of behaviors that can be studied. However, providing power and acquiring data from head-mounted systems remain key bottlenecks, often requiring either a tethered interface that disrupts behavior or a heavy battery that limits recording time. Moreover, extending the duration of recordings requires high light collection efficiency to minimize excitation power and therefore decrease the rates of photobleaching and phototoxicity. Although wireless systems have been developed for low-power neuroscience tools, such as wirelessly powered optogenetic stimulators and wireless local field potential recording systems, fully wireless power and data transmission for high-power devices, including image sensors, remains a major challenge, especially in small rodent-sized form factors.

Here, we present a fully wireless one-photon Miniscope for long-term neural recordings, integrating novel wide-range wireless power transfer, free-space optical data transfer, and upgraded optics for improved light collection efficiency. Unlike previous battery-based, wire-free, miniaturized microscopes, our approach enables continuous recording without a predefined time limit by remotely delivering power via a Quasistatic Cavity Resonance (QSCR) transmitter (over 500 mW power delivery within a 2,500 cm<sup>2</sup> area). The custom miniaturized optical communication system supports real-time data transfer (up to 10 Mbps) and processing, while enhanced optical throughput and sensitivity (5x improvement over our previous Miniscope V4 generation) extend imaging duration without inducing photobleaching. Initial validations using a 2,500 cm<sup>2</sup> open-field test with freely behaving mice demonstrate the feasibility of the system for in vivo experiments. By overcoming the limitations posed by wires and batteries, this technology opens up new experimental possibilities, including the long-term recording of complex social behaviors in multiple freely moving animals. We aim for these wireless power and data technologies to be designed into a modular format that can serve as a flexible platform for a wide range of neural recording and modulation devices.

**Disclosures:** T. Sasatani: None. M. Brosch: None. F. Sangiuliano Jimka: None. Z. Dong: None. J. Saunders: None. H. Semwal: None. P. Zhao: None. M. Sehgal: None. L. Oesch: None. A. Guha: None. H. Chorsi: None. K. Keus: None. B.A. Madruga: None. A.K. Churchland: None. P. Golshani: None. D. Aharoni: None.

## **Poster**

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR254.02/ZZ8

**Topic:** J.04. Physiological Methods

**Support:** NIH Grant DP2 MH129986  
JSPS KAKENHI Grant 23K28068  
W.M. Keck Foundation Junior Faculty Award at the David Geffen School of Medicine at UCLA  
Chan Zuckerberg Initiative (CZI) Grant 2024-338522

**Title:** A Modular Platform for Multimodal Biosignal Acquisition in Freely Moving Animals

**Authors:** \*A. BAHRAMI<sup>1</sup>, H. SEMWAL<sup>1</sup>, M. BROSCH<sup>1</sup>, T. SASATANI<sup>2</sup>, D. AHARONI<sup>1</sup>;  
<sup>1</sup>UCLA, Los Angeles, CA; <sup>2</sup>Grad. Sch. of Engin., The Univ. of Tokyo, Bunkyo-ku, Japan

**Abstract:** Multimodal biosignal monitoring is essential for understanding complex neural and physiological processes in freely moving animals. However, most existing systems are bulky, rigidly designed for specific modalities, and lack the flexibility required for diverse experimental paradigms. The acquisition of neural and biological signals in small, freely moving animals greatly benefits from miniaturized, modular platforms capable of supporting diverse sensing, data, and power requirements. To meet these needs, we have developed a compact, reconfigurable electrophysiology (ephys) platform that is capable of simultaneously recording neural and peripheral biosignals while also allowing for flexible integration of sensing modalities, data interfaces, and power sources. At the core of our design is a  $9 \times 9$  mm<sup>2</sup> custom “motherboard” based on an ARM Cortex-M4F microcontroller (120 MHz, 1 MB Flash, 256 KB SRAM). This motherboard interfaces with stackable peripheral modules that deliver electrophysiology, electrocardiography (ECG), electromyography (EMG), and environmental sensing capabilities. A high-density electrode interface board interfacing with an onboard Intan RHD2132 ephys chip provides up to 32 channels of electrophysiology recording in a small footprint. High-throughput data transmission is supported in three ways: (1) wired low-voltage differential signaling (LVDS) to external receivers, (2) wireless near-infrared optical communication at rates up to 12 Mbit/s, and (3) on-board microSD storage handling up to 25 MB/s. Power can be delivered via a tethered connection, onboard lithium-polymer (LiPo) battery, or wide-range wireless power transfer systems, enabling untethered operation when needed. Initial prototype evaluations confirm stable neural data acquisition over extended recordings and robust performance of the wired communication link. These results demonstrate that our modular ephys platform can accommodate complex multimodal experiments while minimizing the size and weight imposed on freely moving animals. This work presents a scalable, miniaturized electrophysiology platform that prioritizes modularity across sensors, data channels, and power domains—advancing dense, multimodal biosignal monitoring in freely moving animals with minimal physical and physiological impact.

**Disclosures:** A. Bahrami: None. H. Semwal: None. M. Brosch: None. T. Sasatani: None. D. Aharoni: None.

**Poster**

**PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR254.03/ZZ9

**Topic:** J.04. Physiological Methods

**Support:** DGSOM W. M. Keck Junior Faculty Award  
JSPS KAKENHI Grant Number 23K28068  
Department of Defense National Defense in Science and Engineering  
Fellowship

**Title:** Enabling Long-Term, Multi-Region Brain Imaging in Freely Behaving Animals with the Miniscope-UltraSmall

**Authors:** \*H. SEMWAL<sup>1</sup>, T. SASATANI<sup>5</sup>, B. ZANAGAR<sup>6</sup>, J. SAUNDERS<sup>2</sup>, M. BROSCH<sup>1</sup>, F. SANGIULIANO JIMKA<sup>2</sup>, Z. DONG<sup>3</sup>, A. BAHRAMI<sup>2</sup>, D. AHARONI<sup>4</sup>;

<sup>1</sup>Neurol., <sup>2</sup>UCLA, Los Angeles, CA; <sup>3</sup>UCLA, New York, NY; <sup>4</sup>Dept. of Neurol., UCLA, Los Angeles, CA; <sup>5</sup>Dept. of Electrical Engin. and Information Systems, The Univ. of Tokyo, Bunkyo-ku, Japan; <sup>6</sup>Neurol., UCLA Chapter, Los Angeles, CA

**Abstract:** Neurobehavioral imaging in freely behaving animals aims to uncover how complex behaviors arise from populations of neurons and their associated circuits. Miniaturized, head mounted microscopes (miniscopes), have enabled neural activity recorded from large populations of neurons using genetically encoded calcium indicators (GECI) in freely behaving animals. However, limitations in current technology, such as size, weight, and tethering, restrict the recording times and inhibit naturalistic experimental setups. As paradigms shift towards longer recording sessions in naturalistic environments from multi-site or multi-animal recordings, the technology underlying miniscopes is under active development. Leveraging advances in modern optics and small scale sensors, we introduce the Miniscope-UltraSmall (MSUS), a next-generation device in the UCLA Miniscope ecosystem.

The MSUS features a novel optical pathway with an 800  $\mu\text{m}$  diameter field of view, a small form factor (7.0 x 8.0 x 4 mm), and weighs less than 250 mg, making it around 1/10th the size and weight of our previous generation Miniscopes. The MSUS incorporates an electronic imaging plane adjustment capable of  $\pm 75 \mu\text{m}$  and imaging resolution to resolve single cell bodies ( $< 3 \mu\text{m}$ ). Due to its reduced size and footprint, the MSUS is ideally suited for simultaneous recordings across multiple brain regions, studies of social interaction and natural behaviors, and long-term recordings spanning behavior and sleep.

Designed around low-power electronics, the MSUS will support wireless power transfer across behavioral spaces, eliminating the need for tethers and increasing the size and complexity of experimental setups. This also makes neural recordings in new paradigms possible, including aviary species (e.g. songbirds or bats), as well as naturalistic, larger environments. The MSUS will be open-sourced after completion of internal validation with an aim to democratize access to neuroscience and lower the barrier to record neural data. By continuing to reduce the size, weight, and cost, we hope to enable a new generation of neuroscientific recordings, spanning social, multi-site, and long-term recordings.

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## Poster

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR254.04/ZZ10

**Topic:** J.04. Physiological Methods

**Support:** STIMscope: 5U01NS126050  
DGSOM W. M. Keck Junior Faculty Award

**Title:** MiniSTIM: a miniaturized one-photon miniscope for spatiotemporal neural imaging and modulation

**Authors:** \*F. SANGIULIANO JIMKA<sup>1,2,3</sup>, L. T. OESCH<sup>4</sup>, Y. LIU<sup>2</sup>, S. WANG<sup>5</sup>, A. K. CHURCHLAND<sup>4</sup>, H. T. BLAIR, IV<sup>5</sup>, P. GOLSHANI<sup>2</sup>, D. AHARONI<sup>2</sup>;  
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**Abstract:** In recent years, miniaturized one-photon microscopes have become vital tools in behavioral neuroscience, enabling researchers to study neural circuits in freely moving animals. Initially designed for widefield calcium imaging, these systems have evolved to include features such as integrated electrophysiology, multi-channel imaging, and optogenetic capabilities, yet still face limitations that hinder the scope of freely behaving animal experiments. An example of this is our previously developed UCLA Miniscope Version 4 (V4) which has been widely adopted for its ease of use, affordability, and large support community. Yet, even with advancements made over the past decade, there are still many unmet experimental and technical challenges to be overcome in order to support the demands of modern neuroscience investigation. Here, we introduce the MiniSTIM, a miniaturized one-photon SpatioTemporal Imaging Microscope with new electrical and optical designs to support multi-channel spatiotemporal illumination in freely behaving animals.

The MiniSTIM features a 5 MP back-illuminated image sensor with MIPI CSI-2 protocol and a 6 Gbps serial communication link supporting high-resolution video transmission, high-bandwidth bidirectional control, and power delivery (up to 6 watts), all over a single, flexible coaxial cable. The MiniSTIM optics have been designed to achieve a 1.7 mm diameter field-of-view, 1 mm working distance, and up to a 70-fold increase in sensitivity over our Miniscope V4. Control and acquisition is powered by a Nvidia Jetson Orin and can support up to 4 streaming devices (MiniSTIMs, Miniscopes, MiniCAMs) simultaneously. A key innovation of the MiniSTIM is the integration of high-density microLED display panels that handle both patterned excitation and optogenetic stimulation, enabling efficient dual-functionality within a compact system. Single-photon patterned excitation imaging can improve signal-to-noise and axial resolution while patterned optogenetic stimulation, at a separate wavelength, can deliver near-single-cell resolution stimulation for real-time, closed-loop experiments.

We validated the MiniSTIM's design through bench testing and demonstrate in vivo imaging of the anterior cingulate cortex (ACC) in a mouse with a 1 mm GRIN lens, capturing both widefield

and targeted imaging of neuronal patches. The MiniSTIM enables simultaneous high-resolution imaging and precise patterned optogenetics in freely behaving animals, offering new opportunities to causally dissect neural circuit dynamics with fine spatiotemporal control.

**Disclosures:** F. Sangiuliano Jimka: None. L.T. Oesch: None. Y. Liu: None. S. Wang: None. A.K. Churchland: None. H.T. Blair: None. P. Golshani: None. D. Aharoni: None.

## **Poster**

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

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**Topic:** J.04. Physiological Methods

**Support:** NIH 4DP2MH129986  
DGSOM W. M. Keck Junior Faculty Award

**Title:** Indeca: towards robust and interpretable deconvolution for calcium imaging

**Authors:** \*Z. DONG, D. AHARONI;  
Neurol., UCLA, Los Angeles, CA

**Abstract:** Calcium imaging enables monitoring of neuronal activity, but accurate deconvolution of calcium signals remains a major challenge. Conventional methods often yield noisy, continuous signals prone to overfitting, necessitating manual parameter tuning. Furthermore, post-hoc thresholding are required to infer spikes from deconvolved signals. We introduce InDeCa (Interpretable Deconvolution for Calcium Imaging), a novel algorithm that directly estimates binary spike trains while avoiding overfitting without the need for explicit regularization. This is achieved by convexifying the binary deconvolution problem with a thresholding process that naturally discourages overfitting. InDeCa also supports integer spike inference via temporal upsampling, and further reduces noise sensitivity through an error-weighting scheme. Additionally, InDeCa leverages the inferred spikes to iteratively refine and denoise a bi-exponential calcium kernel, yielding interpretable time constants that can be easily evaluated. By integrating thresholding, upsampling, error weighting, and spike-informed kernel estimation, InDeCa enhances both the accuracy and interpretability of spike inference. We validated InDeCa on simulated datasets and benchmarked it against popular deconvolution approaches using ground truth recordings spanning diverse calcium indicators and brain regions. Our results show that InDeCa consistently performs well across datasets with minimal parameter tuning, providing a robust and interpretable framework for spike inference in calcium imaging.

**Disclosures:** Z. Dong: None. D. Aharoni: None.

## **Poster**



## **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

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**Topic:** J.04. Physiological Methods

**Support:** NIH 5U01NS126050  
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**Title:** STIMscope: closed-loop real-time imaging and patterned optogenetics at single-cell resolution

**Authors:** \*H. CHORSI<sup>1</sup>, Y. JIN<sup>2</sup>, S. SOLDADO-MAGRANER<sup>3</sup>, A. ZHENG<sup>4</sup>, I. SOLTANALIPOURYEKESAMMAK<sup>4</sup>, F. SANGIULIANO JIMKA<sup>2</sup>, D. V. BUONOMANO<sup>3</sup>, P. GOLSHANI<sup>2</sup>, D. AHARONI<sup>2</sup>;

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**Abstract:** Despite significant advances in optical imaging and optogenetics, neuroscience still lacks accessible platforms that offer true closed-loop, real-time control. Such systems—capable of simultaneous imaging and adaptive, activity-driven intervention—could transform how we probe and influence neural circuits in action. By merging real-time analysis with feedback-based stimulation, these tools promise new insights into brain connectivity, plasticity, disease mechanisms, and therapeutic development. However, several key challenges remain, including the need for fast, single-cell resolution imaging and processing; minimal feedback latency; precise synchronization between imaging and optogenetic stimulation; robust integration of hardware and software; and a lack of standardized data pipelines for reproducible, scalable research.

To address these gaps, we introduce STIMscope (SpatioTemporal Illumination Microscope), a highly adaptable, large field-of-view (FOV) programmable microscope for single-cell resolution fluorescence imaging and optogenetic manipulation in behaving animals, brain tissue slices, and neuronal cultures. STIMscope features large-aperture imaging optics, a back-illuminated CMOS sensor and Digital Micromirror Device (DMD) for simultaneous imaging and patterned illumination, managed by a centralized control unit for seamless and synchronized operation. STIMscope incorporates a closed-loop, real-time analysis pipeline—CRISPI (Closed-loop Real-time Imaging and Stimulation Pipeline Infrastructure)—leveraging GPU-accelerated computing for activity-driven excitation of the DMD, enabling real-time adjustment and optimization. The dedicated GUI, STIMViewer, streamlines user interaction and visualization. An open-source, standardized data pipeline and structure facilitate reproducible, scalable experiments across labs. All features are integrated into a low-cost (under \$5k), open-source design for broad accessibility.

To demonstrate versatility, we performed closed-loop, large FOV imaging and patterned illumination in 2D stem cell-derived human neurons, and established a “cortical circuit in a dish” to study cortical plasticity and computation in organotypic brain cultures.

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## **Poster**

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

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**Topic:** J.04. Physiological Methods

**Support:** NIH Grant 4DP2MH129986  
NIH Grant 5U01NS126050  
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JSPS KAKENHI Grant 23K28068

**Title:** Cala, mio, & noob: fully integrated streaming calcium imaging and analysis

**Authors:** \*R. W. CHANG<sup>1,2</sup>, J. SAUNDERS<sup>1</sup>, T. SASATANI<sup>4</sup>, M. BROSCHE<sup>1</sup>, Z. DONG<sup>1</sup>, H. SEMWAL<sup>1,3</sup>, D. AHARONI<sup>1</sup>;

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**Abstract:** Naturalistic neuroscientific experiments require us to acquire and analyze long-term multimodal data. Calcium imaging analysis tools are typically monolithic and challenging to integrate with the rest of the tooling used in an experiment. Graph-based frameworks like LabVIEW and Bonsai are widely used for acquisition, but face similar integration challenges. This forces researchers to compromise their experiment workflow around the available tools, instead of utilizing the tools around their experiment designs. We present Cala, a streaming Calcium fluorescence imaging analysis package with a focus on reproducibility, usability, and extensibility. Cala is easy enough to deploy, and efficient enough to run on a laptop without compromising accuracy. Powering Cala is Noob, a streaming pipeline framework for Python that can wrap existing code with minimal adaptation. This allows us to provide high-performance analysis and acquisition tools as structured compositions of smaller operations. Devices and analysis methods are written as composable pipelines that still allow full access to their individual parts, giving researchers much finer control; e.g. patching plotting, I/O, or custom algorithms into a preset pipeline, or creating their own. This design supports both the free-form creativity needed throughout the experimental process and the structure needed for reproducible, standards-driven science. Processing pipelines are declaratively configured with YAML, aiming for a zero-code UI and end-to-end experimental replication from a single file. Leveraging Noob, Cala operates three loops simultaneously: the top layer GUI, the analysis loop that yields the initial pass of fluorescence footprints and traces, and the refinement loop that optimizes both

over longer timescales. Furthermore, it provides clear visibility into data transformations across the entire processing pipeline at the same time. We further show how an integrative pipelining system can be integrated into acquisition hardware and software with our Miniscope I/O SDK Mio. This creates a unified programming interface from photons to figures, dissolving distinctions between analysis vs. acquisition tools and open- vs. closed-loop experiments. By focusing on the glue between tools, rather than building vertically-integrated, single-purpose hardware/software rigs, we facilitate the kind of long-term, heterogeneous, collaborative experiments required to understand the naturally behaving brain.

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## **Poster**

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

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**Topic:** J.04. Physiological Methods

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DGSOM W. M. Keck Junior Faculty Award

**Title:** Sciop & nwb-linkml: resilient data infrastructure in an era of informational crisis

**Authors:** \*J. SAUNDERS<sup>1,2</sup>, H. BRENADO<sup>2</sup>, A. GAY<sup>2</sup>, I. KNAPP<sup>2</sup>, R. LY<sup>3</sup>, A. MENDEZ-PRATT<sup>2</sup>, H. SCHÖNEMANN<sup>4,2</sup>, W.-M. VIERDAG<sup>5</sup>, W. WAITES<sup>6,2</sup>, D. AHARONI<sup>7</sup>;

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National Laboratory, Berkeley, CA; <sup>4</sup>Humboldt University Berlin, Berlin, Germany; <sup>5</sup>Genome Biology Unit, European Molecular Biology Laboratory (EMBL), Heidelberg, Germany;

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**Abstract:** Our archives are too often single points of failure that can disappear in one lapsed funding cycle. This year has shown that fragility is anything but theoretical, with foundational health, climate, and neuroscientific research vanishing from archives overnight. Traditional archives also limit our ambitions for "open data" as a living, collaborative, process - instead data is overwhelmingly used once and stockpiled, frozen in time at the "end" of an experiment. The moment demands we rearchitect our informational systems in every domain of research from the benchtop to the library.

We will present our work across two of those domains:

1) as sciop: we are responding to immediate crisis with hybrid peer-to-peer/federated archives. With thousands of participants contributing whatever they can, sciop is a different kind of

archive that is rapidly eclipsing the scale and flexibility of our largest data repositories. We will show ongoing work extending and bridging the peer-to-peer BitTorrent and federated ActivityPub protocols with the arbitrary metadata of the Semantic Web to make a new kind of distributed archive without single points of failure.

2) as nwb-linkml: we are redesigning neuroscientific data formats for distributed, fluid use spanning experimentation and archives. We use linkml to unbundle the typically vertically-integrated data standards stack, modularizing schemas, implementations, and formats, giving a clear path towards interoperability between diverse biomedical data formats. We will show work that allows NWB to be stored in flexible, lightweight metadata files with arbitrary backends for arrays, rendering NWB as a chunked, content-addressed format suitable for a new generation of metadata-enriched p2p protocols.

Together, these two pieces hint at how reimagining archives and data formats can dissolve basic problems in research data management: there is no need for "conversion" to a format when the format supports fluid schemas that can evolve along with the experiment while maintaining rigor. There is no need for a separate archival step when your data is shared from the moment it's acquired in federated archives that span scales from labs to disciplines. There is no risk of our work disappearing when we rebuild our data infrastructures to reflect the social nature of its production, where communication and distribution is built into every stage of the research lifecycle.

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## **Poster**

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR254.09/ZZ15

**Topic:** J.04. Physiological Methods

**Title:** Development of automated femtosecond fiber delivery for multi-photon microscopy

**Authors:** \***J. N. MASTRON;**

Applications Sci. and Product Mgmt., TOPTICA Photonics, Inc., Pittsford, NY

**Abstract:** Completely replacing free-space optical paths between a Watt-level femtosecond laser and a two-photon microscope with fiber coupling is a game-changer for modern microscopy. Integrating new advancements in optical fibers, such as Polarization-maintaining hollow-core fibers that are now commercially available, allows the delivery of femtosecond pulses directly from the laser source to the microscope, enabling new microscope designs. Further, the fiberization of laser beam delivery brings laser safety and ease of use for ultrafast lasers up to the same level as established CW laser systems.

In combination with TOPTICA's COOL-AC technology, a hands-off, automated fiber coupling is developed that eliminates manual alignment at installation, optimizes fiber coupling at the touch of a button, and monitors fiber coupling efficiency internally without the need for external tools or equipment.

In collaboration with external research groups, we have demonstrated a number of applications that directly benefit from ultrafast fiber coupling. Miniaturized, light-weight microscopes can be head-mounted on freely moving animals in order to study neuronal activity with minimal influence on the animal's natural behavior. Endoscopic or hand-held devices can be equipped with non-linear imaging capabilities otherwise impossible without fiber coupling. Thirdly, maneuverable microscopes, which can rotate in almost every angle around the sample, potentially even mounted on robotic arms, provide new flexibility and access to samples.

**Disclosures:** J.N. Mastron: A. Employment/Salary (full or part-time): TOPTICA Photonics, Inc..

## **Poster**

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

**Location:** SDCC Halls B-H

**Time:** Monday, November 17, 2025, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR254.10/ZZ16

**Topic:** J.03. Anatomical Methods

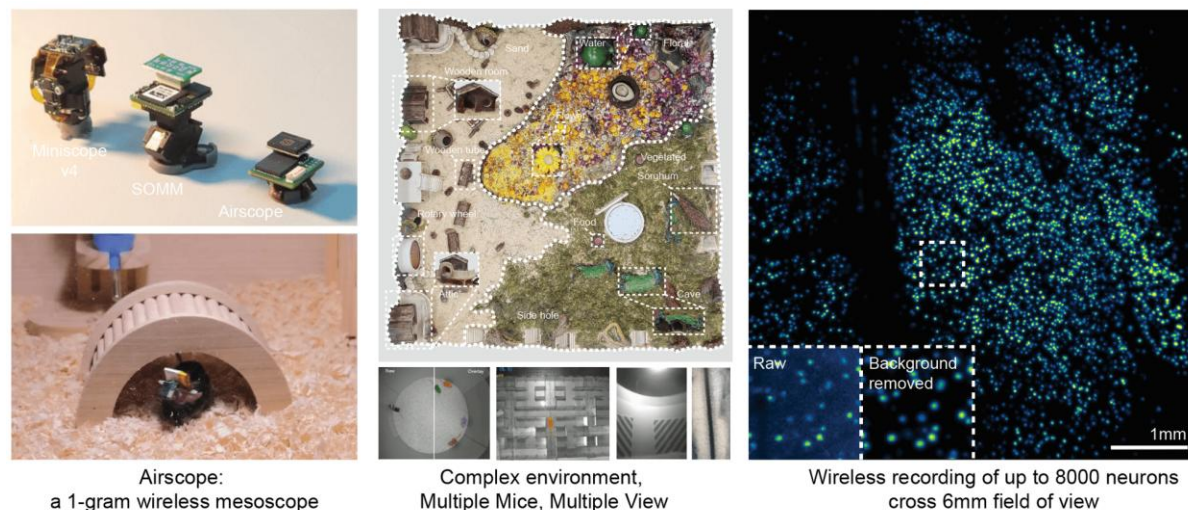
**Title:** A 1-gram wireless microscope for mesoscopic neural observation during fully unconstrained behavior

**Authors:** \*L. YUAN<sup>1,2</sup>, A. LI<sup>3</sup>, M. WANG<sup>1</sup>, W. ZHAO<sup>4</sup>, Y. ZHANG<sup>5</sup>;

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**Abstract:** To truly grasp the complex neural dynamics underlying natural behavior, it is essential to observe neural circuits in action at single-neuron resolution and in the context of an animal's interaction with its environment and conspecifics. We developed Airscope, a wireless mesoscope weighing only 1 gram that delivers 4  $\mu\text{m}$  resolution across a 6 $\times$ 6 mm<sup>2</sup> field of view—encompassing half the mouse cortex. By integrating compact aspherical optics with high-throughput wireless acquisition hardware, Airscope enables the recording of up to 8,000 neurons in freely moving mice—a 25-fold increase over previous wireless neural recording systems. Combined with SAM2Mice, a zero-shot semantic behavior tracking tool, Airscope enables investigation of the neural basis of unconstrained behavior in complex, naturalistic environments and social settings. We demonstrated brain-wide neural recordings as multiple mice freely explored a large (2 $\times$ 2 m<sup>2</sup>) semi-naturalistic habitat, engaged in complex decision-making in a large-scale labyrinth, and interacted in diverse social contexts. Its compact form further allowed synchronized multi-site recordings by mounting multiple devices on a single mouse—including

simultaneous brain-spinal cord and brain-facial activity imaging. With large-scale recordings during fully unlocked full behavioral repertoire and unbiased natural behavior, Airscope serves as a powerful tool to reveal the neural mechanisms underlying complex behaviors.



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## Poster

### PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice

**Location:** SDCC Halls B-H

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**Program #/Poster #:** PSTR254.11/ZZ17

**Topic:** J.04. Physiological Methods

**Support:** NIH Grant R15NS135507

**Title:** Commutator-assisted fiber bundle imaging system for neural and behavioral recording in freely behaving animals

**Authors:** D. SHEN<sup>1</sup>, L. ZHAO<sup>1</sup>, J. WANG<sup>1</sup>, D. EKANAYAKE<sup>2</sup>, K. NAGAMOTO-COMBS<sup>2</sup>, \*B. LIANG<sup>1</sup>;

<sup>1</sup>Univ. of North Dakota, Grand Forks, ND; <sup>2</sup>Univ. of North Dakota, Grand Forks, ND.

**Abstract:** Neuroscience experiments often require the recording and/or modulation of neural activity in naturalistic contexts to gain insights into the neural mechanisms underlying complex behaviors. Miniaturized optical imaging systems, combined with genetically encoded indicators, have become widely used tools for studying brain circuit dynamics during naturalistic behaviors

in various animal models. In addition to wide-field miniature microscopes and single optical fiber-based systems, fiber bundle-based imaging systems, utilizing either single-photon or two-photon light sources, have also been developed to optically record or modulate the activity of neurons and glial cells in freely behaving mice. While fiber bundle-based systems enable structured illumination for single-cell optogenetic modulation, they are limited in freely behaving animals due to tether twisting caused by restricted rotation. Although custom commutators and electrical-tether-based solutions have been proposed, they either complicate image processing or are incompatible with fiber bundles. To address these challenges, we describe a compact fiber bundle imaging and optogenetic modulation system that dynamically adjusts the position of the entire optical assembly in response to the animal's movements, including translation and rotation. Our system incorporates torque sensing with a Hall sensor at the proximal end of the fiber bundle, coupled with a motorized rotary stage to rotate the optical system accordingly. A slip ring is used to provide power and enable rotation, while imaging data is managed by an onboard microcomputer integrated with the optical assembly, eliminating the need to transmit high-bandwidth data through the slip ring, which typically lacks sufficient throughput. This system complements existing miniaturized optical imaging tools and offers a new paradigm for experiments requiring imaging and/or modulation of neural activity in freely behaving animals.

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## **Poster**

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

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**Title:** Chronic deep-brain imaging through a hair-thin holographic endoscope

**Authors:** M. STIBUREK<sup>1</sup>, T. PIKÁLEK<sup>1</sup>, P. ONDRACKOVA<sup>1</sup>, A. LORENZ<sup>2</sup>, B. MURTHY<sup>4</sup>, J. U. HENSCHKE<sup>4</sup>, K. HERZÁNOVÁ<sup>1</sup>, E. L. MAROSI<sup>4</sup>, P. KOLBÁBKOVÁ<sup>1</sup>, H. JIA<sup>4</sup>, S. MIKULOVIC<sup>4</sup>, J. M. PAKAN<sup>4</sup>, A. ATTARDO<sup>4</sup>, \*H. UHLIROVA<sup>1</sup>, T. CIZMAR<sup>3</sup>;

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**Abstract:** Holographic endoscopy leverages a hair-thin multimode optical fiber to enable sub-cellular resolution optical imaging of hard-to-reach locations or deep within scattering tissue [1]. This technology is transformative for neuroscience as it allows synaptic and cellular investigations within the intact brain, where physiological function relies heavily on the preserved connectivity of neural circuits spanning the entire brain. While previous work demonstrated holographic endoscopy optical imaging of neuronal connectivity, calcium transients and blood flow in anesthetized mice [2], even with its ultra-thin profile, acute implantation of any probe inevitably causes tissue perturbation. This can significantly interfere with functional imaging modalities such as intracellular calcium signaling and blood flow, making tracking of the same structures for an extended period of time infeasible.

Here we present recent advances which address this limitation with a novel endoscopic platform. We not only demonstrate structural and functional holographic endoscopy optical imaging deep in the brain of live mice over several weeks both in anesthetized and awake mice but also investigate synaptic dynamics in a fashion that has been impossible with other existing methods.

References:

[1] Uhlirova H et al., Neurophotonics. 2024

[2] Stiburek M et al., Nat Commun. 2023

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## Poster

### **PSTR254: Optical Methodology: Development: Single Photon Endoscopy in Head Fixed and Freely Moving Mice**

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the MEYS of the CR (CZ.02.1.01/0.0/W0.o0k/e1g5at0e03/0000476 and CZ.02.1.01/0.0/0.0/16 013/0001775)  
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**Title:** Simultaneous Opto-Electrical Recording in Deep Brain Tissue Using Multimode Fibre-Based Endoscopy

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**Abstract:** Electrical recordings remain a cornerstone of neuroscience research, providing high temporal resolution for monitoring neural activity. However, electrophysiological techniques do not reveal the morphology or identity of active cells. Optical methods such as fluorescence imaging can help address this limitation, but their use in deep brain regions is restricted by light scattering and absorption. Endoscopy based on multimode fibres has recently emerged as a promising approach for minimally invasive deep-brain imaging. It enables the collection of fluorescent signals with subcellular resolution and negligible tissue disruption. However, combining optical and electrical recordings from the same brain region often requires inserting additional electrodes near the optical probe, which increases tissue damage and reduces recording stability. To address this challenge, we present an integrated opto-electrical probe based on a multimode fibre system combined with an ultrathin, minimally invasive electrode array. The compact design enables chronic, simultaneous optical and electrical recordings from deep brain regions in vivo.

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