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Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.01/D1

Topic: A.06. Developmental Disorders

Title: Investigation of social dominance and underlying neurocircuitry in Autism Spectrum Disorder

Authors: *A.-M. ABBAN-DEMITRUS, K. MCCARTHY, Q. WU, H. HUANG, H. MAN; Boston Univ., BOSTON, MA

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction, altered communication and compulsive, repetitive behaviors. However, ASD comorbidities such as deficits in the establishment of social hierarchy formation are less studied. Individuals with autism are unable to engage in prosocial behaviors such as strategic partnership and alliance formation, which impairs social mobility and participation in hierarchical social dynamics. This exacerbates their vulnerability to social expulsion and systemic oppression. To characterize social dominance and associated neurocircuitries in ASD, we employed a murine model overexpressing a major ASD gene, *Ube3A*. The *Ube3A* gene, which resides on chromosome 15q11-13, encodes UBE3A which is an E3 ubiquitin ligase while also serves as a transcriptional co-regulator. Clinical data shows that over 70% of individuals with maternally inherited duplication of *Ube3A* are diagnosed with autism. Transgenic mice with 2 additional copies of *Ube3A* display the core autistic traits, further demonstrated by our findings from key behavioral and molecular tests. Using the well-established tube test for social dominance, we observed increased social dominance and rank among the ASD *Ube3A* 2X mice. These findings were confirmed by a second assay, water-based platform test of social dominance. Analysis of dominance strategies reveal significantly decreased retreat attempts in the *Ube3A* 2X mice. To observe the role of retreat in this hyper-dominance trait, we obstructed the middle of the tube and timed exit latencies. Our results demonstrated increased latencies to withdraw, signaling that this ASD hyper-dominance trait is linked to reduced retreat tendencies ($n>10$). cFos immunostaining showed increased activity in mPFC neurons and decreased activity in a novel region, the basal pontine nucleus (BPN) in the 2X mice ($n=3$). These findings were confirmed in the TRAP2:AI14 transgenic line, which expresses a tdTomato reporter upon neuronal stimulation. To probe the functional role of these regions, we suppressed activity of mPFC by hM4Di in 2X animals and found a decrease in social dominance. Conversely, hM4Di suppression of neuronal activity in the BPN in WT subordinate animals resulted in increased dominance. Furthermore, fiber photometry tracking of BPN activity in WT mice showed increased BPN activity in the loser, and decreased BPN activity in the winner ($n=2$). Overall, these findings indicate alterations in social hierarchy and reveal the related neurocircuitry in *Ube3A* ASD.

Disclosures: A. Abban-Demitrus: None. **K. McCarthy:** None. **Q. Wu:** None. **H. Huang:** None. **H. Man:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.02/D2

Topic: A.06. Developmental Disorders

Title: Developmental Reorganization of Phenotypic Architecture in Autism Spectrum Disorders

Authors: *A. FERNANDEZ;
Hlth. and Biomed. Sci., Univ. of Texas Rio Grande Valley, Brownsville, TX

Abstract: Autism spectrum disorder (ASD) is characterized by substantial variation across sensory, repetitive, motor, social-communication, and psychopathology domains. Although these behavioral dimensions frequently co-occur, it remains unclear whether some play a more central role in organizing the broader autism phenotype and whether this organization changes across development. Using phenotypic data from the SPARK cohort, the largest autism research registry to date, we examined associations among behavioral dimensions and outcomes spanning psychopathology, social functioning, and autism symptom severity across childhood, adolescence, and adulthood. Sensory-repetitive features emerged as the most influential dimensions within the autism phenotype, showing broader and stronger associations across behavioral outcomes than motor or social-communication features. Repetitive behavior measures consistently occupied the highest positions in the behavioral hierarchy, whereas social-communication features showed comparatively restricted influence. These patterns were highly reproducible across independent subsamples and remained evident after accounting for anxiety symptoms.Developmental analyses revealed a marked reorganization of behavioral organization across the lifespan. During childhood (ages 4-12), sensory-repetitive features occupied the most central positions within the phenotype. This pattern shifted across adolescence, and by adulthood (18+), motor features emerged as the dominant dimensions. Comparisons across age groups demonstrated high stability within childhood but substantially lower similarity between childhood and adulthood, indicating a systematic developmental reorganization of phenotypic structure. These findings suggest that the behavioral dimensions most central to the autism phenotype change systematically across development, highlighting the importance of considering developmental stage when characterizing autism and its associated features.

Disclosures: A. Fernandez: None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.03/D3

Topic: A.06. Developmental Disorders

Title: Elucidating early-life behavioral biomarkers of Autism Spectrum Disorder in an idiopathic and syndromic mouse model

Authors: J. LUNA[1], *M. BINDER[2];
[1]Psychology, [2]Trinity Univ., San Antonio, TX

Abstract: Autism Spectrum Disorder (ASD) is a common neurodevelopmental condition that presents with repetitive behaviors and social and communicative deficits which significantly worsen individuals' quality of life. Early detection and therapeutic intervention yield a better long-term prognosis, however, due to a lack of tools, ASD is not diagnosed until well after significant milestones have passed, creating a need to identify early life behavioral biomarkers. To address this need, we assessed neonate's gait, sensory function, grip strength and ultrasonic vocalizations (USVs) in response to a noxious stimuli in three different mouse models: wild-type C57BL/6J mice, BTBR mice (an idiopathic model of ASD), and *Cntnap2*$^{-/-}$ mice (a syndromic model of ASD). When assessing gait, we found that ASD models had a significantly larger width of their stride relative to controls. BTBR mice also had an increased stride length compared to the other groups. In the sensory paradigm, C57 mice preferred rough over smooth textures whereas *Cntnap2*$^{-/-}$ displayed hypersensitivity, favoring smooth textures, whereas BTBR mice had no texture preference indicative of hyposensitivity. For grip strength, BTBR pups displayed a shorter latency to fall relative to the other conditions. When assessing USVs in response to a noxious stimuli, C57 mice displayed a reduction in USV number, whereas no differences in USV production were found across either ASD strains. Altogether, our study identified various early life behavioral biomarkers pertinent to both idiopathic and syndromic ASD, which may aid in the creation of novel diagnostic tools.

Disclosures: J. Luna: None. **M. Binder:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.04/D4

Topic: A.06. Developmental Disorders

Support: SFARI Grant 946867
NIMH Grant MH118500

Title: Structural changes in autism reflect atypical brain network organization and phenotypical heterogeneity: a hybrid deep network approach

Authors: *S. LOKRAY[1,2], B. ZIKOPOULOS[1,3,4,5,6], A. YAZDANBAKHSH[1,2,4,6];
[2]Computat. Neurosci. and Vision Laboratory, Dept. of Psychological and Brain Sci., [3]Human Systems Neurosci. Laboratory, Dept. of Hlth. Sciences, Program in Human Physiol., [4]Grad. Program for Neurosci., [5]Dept. of Anat. & Neurobiology, Boston Univ. Sch. of Med., [6]Ctr. for Systems Neurosci., [1]Boston Univ., Boston, MA

Abstract: Autism Spectrum Disorder (ASD) is a developmental disorder exhibiting marked heterogeneity in social and emotional responses, language, and behavior, typically assessed with diagnostic scales, such as the Social Responsiveness Scale (SRS). Convolutional Neural Networks (CNNs) have increasingly been applied to neuroimaging data, including structural MRI (sMRI), to classify ASD and identify atypical brain features. However, the relationship between structural brain changes observed in sMRI, the affected brain functional networks inferred from these structural changes, and their connection to ASD phenotypes and scores is not characterized and requires systematic investigation. To address this issue, we used 3D CNNs with gradient based explainability methods to dissect macrostructural changes in ASD. Using T1-weighted sMRI from the ABIDE II repository, our 3D CNN was able to distinguish between high- and low-severity ASD scans with ~77% accuracy. We then extracted voxel-level saliency maps to identify and correlate structural changes with SRS scores. We found dominant involvement in ASD of regions in (a) the left hemisphere and (b) the frontal and temporal lobes, which are associated with the default mode, salience, and language networks. Our findings highlighted brain network similarities and differences between high and low severity ASD and showed that typically developed brains fall at the low-severity end of the high-to-low severity spectrum of ASD. Our bottom-up approach utilized the phenotypic heterogeneity and spectral nature of ASD to uncover significant structural changes across brain regions and functional networks, correlating the structural, functional, and phenotypical heterogeneity of individuals with ASD. This approach enabled us to identify known and novel localized brain regions and global network changes in ASD in relation to phenotypes and clinical scores that can guide diagnostic subtyping.

Disclosures: S. Lokray: None. **B. Zikopoulos:** None. **A. Yazdanbakhsh:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.05/D5

Topic: A.06. Developmental Disorders

Support: NIH MOSAIC R00 (NINDS): 4R00NS130018-03
Gilead Innovation Initiative Summer Research Award

Title: Validating a Valproic Acid Model of ASD to Study the Role of Microglia in the Brain

Authors: *A. J. KRUMBEIN, N. J. SILVA;
Biol., San Francisco State Univ., San Francisco, CA

Abstract: Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental disorder that is characterized by behavioral changes. Genetic and pharmacological animal models in mice and zebrafish recapitulate aspects of the cellular and behavioral phenotypes associated with ASD. Zebrafish share 70% genetic homology to humans and are increasingly used to study ASD. Valproic acid (VPA) is a widely used pharmacological agent for inducing ASD-like phenotypes in vertebrate models, including zebrafish. To study neuroimmune interactions in the brain, we first validated the VPA model and characterized behavior using the DanioVision system pipeline. We report that zebrafish exposed to VPA at 0μM, 1μM, 3μM, and 5μM doses showed no changes in movement, velocity, and habituation learning throughout development. Interestingly, social interaction was altered in VPA-treated fish, as measured using a novel high-throughput assay, termed a fishbook assay. In addition, we found that the predominant immune cell of the brain, microglia, was increased in VPA brains. Our results validate the VPA model and establish a role for microglia to further investigate neuroimmune mechanisms associated with ASD.

Disclosures: A.J. Krumbein: None. **N.J. Silva:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.06/D6

Topic: A.06. Developmental Disorders

Support: NRF grant RS-2024-00398768
KEIT and MOTIE grant RS-2024-00432143
KIST grant 26E0122
KIST grant 26E0131

Title: Real-time rodent behavior classifier using color-based body segmentation (R2C2) for neurodevelopmental disorders

Authors: *H. KIM[1,2,3], A. SERIKOV[1,2,3], C. LEE[1], J. KIM[1,2];
[1]Brain Sci. Inst., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Div. of Bio-medical Sci. & Technology, KIST School, Univ. of Sci. and Technol., Seoul, Korea, Republic of; [3]These authors contributed equally, Seoul, Korea, Republic of

Abstract: Precise classification of behavioral actions is essential for identifying how neuronal activity relates to specific behaviors. This is particularly important for neurodevelopmental disorder models, such as autism spectrum disorder (ASD), in which subtle differences in repetitive or stereotyped behaviors may reflect distinct underlying neural mechanisms. However, conventional behavioral analysis often relies on manual scoring by human observers, which

renders behavioral classification vulnerable to observer-specific bias. To improve the reliability and scalability of behavioral quantification, artificial intelligence (AI)-based methods have increasingly been developed for automated behavioral analysis. Nevertheless, many current approaches still require multi-step workflows, including pose estimation, skeletal-based motion detection and additional computational steps to convert movement features into discrete behavioral classes, often with substantial training datasets and high computational demands. Here, we present Real-time Rodent Behavior Classifier using Color-based Body Segmentation (R2C2), a lightweight end-to-end system for real-time rodent behavior classification. R2C2 uses hue, saturation and value (HSV)-domain color segmentation based on color differences in fur and exposed skin to track rodent body parts and extract movement-based features. By combining HSV-based body-part segmentation with wavelet transform-based feature extraction and a convolutional neural network (CNN) classifier, R2C2 substantially reduces computational requirements while preserving behaviorally relevant information for classification. R2C2 achieved behavioral classification performance comparable to that of expert human observers and successfully differentiated subtle behavioral patterns associated with mouse models of autism spectrum disorder (ASD). By enabling reliable auto-labeling of fine-scale animal actions and behavioral motifs in individual animals, R2C2 may help dissect complex ASD-related behavioral phenotypes and facilitate studies linking behavioral alterations to their underlying neural mechanisms.

Disclosures: H. Kim: None. **A. Serikov:** None. **C. Lee:** None. **J. Kim:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.07/D7

Topic: A.06. Developmental Disorders

Support: Texas Woman's Univerisity Woodcock Institute
Texas Woman's University Startup Funds

Title: Early Environmental Enrichment May Mitigate ASD-Like Behavioral Deficits in Mouse Model of ASD.

Authors: *P. FRAYRE[1], S. VASQUEZ[1], E. NA[2];
[1]Texas Women's Univ., Denton, TX; [2]Texas Woman's Univ., Denton, TX

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communications, learning, and behavior. Prevalence in ASD has risen from 1 in 36 children in 2020 to 1 in 31 children in 2022, according to the CDC. Despite increasing ASD prevalence and awareness, it is still unclear how early interventions may improve symptoms associated with ASD. To better understand this, we utilized a mouse model of ASD in which methyl-CpG binding protein 2 (MeCP2) is knocked out (KO) in glutamatergic

forebrain neurons. . MeCP2 is an epigenetic regulator linked to social and behavioral deficits commonly found in ASD. MeCP2 KO and wild-type mice (WT) were housed in either group-housed environmentally enriched cages (EE) consisting of toys, textures, access to running wheel or single housed (SH) without access to enrichment. After 12 weeks, anxiety-like behavior was assessed through elevated plus maze (EPM) and dark-light test (DLT) as well as social interaction (SI). KO-EE mice demonstrated a decrease in anxiety-like behaviors and increased social interaction, relative to KO-SH. Additionally, hippocampal brain derived neurotrophic factor (BDNF) levels were also significantly increased in KO-EE mice, suggesting improved synaptic plasticity. These findings suggest that early environmental intervention may mitigate ASD behavioral deficits and promote hippocampal BDNF levels in a mouse model of ASD.

Disclosures: P. Frayre: None. **S. Vasquez:** None. **E. Na:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.08/D8

Topic: A.06. Developmental Disorders

Support: Genetic Autism Alliance.

Title: Pathogenic synaptotagmin-1 mutation in mouse hippocampus disrupts synaptic transmission and produces autistic behaviors

Authors: X. GUO[1], Z. WANG[2], A. RAJOOLDEZFULY[3], A. SAFAEI[4], B. YU[2], J. ZHOU[5], H. NISHIMUNE[6], *D.-P. LI[2], D. ARNOLD[3];
[1]Med., Univ. of Missouri, COLUMBIA, MO; [2]Univ. of Missouri, Columbia, MO; [3]Univ. Of Missouri, Columbia, Columbia, MO; [4]Univ. of Missouri-Columbia (SSO), Columbia, MO; [5]Univ. of Florida, Gainesville, FL; [6]Physical Med. and Rehabil., Univ. of Missouri, Sch. of Med., Columbia, MO

Abstract: Mutations in the Ca^{2+}-sensing C2A or C2B domain of synaptotagmin-1 (*SYT1*), a presynaptic Ca^{2+} sensor essential for synchronous neurotransmitter release, cause a rare *SYT1*-associated neurodevelopmental disorder (*SYT1*-NDD) characterized by intellectual disability, motor abnormalities, and features of autism. However, few experimental animal models carrying pathogenic *SYT1* mutations are available to test potential therapeutics. Thus, we developed a mouse model by overexpressing the human disease-associated mutant *SYT1*-D366E in the hippocampus through hippocampal injection of adeno-associated virus 9 (AAV9) carrying mutant *SYT1*, and then evaluated behavioral and synaptic alterations. *SYT1*-D366E overexpression, confirmed by increased *SYT1* protein levels, impaired sociability and social novelty preference compared with control vector-expressing mice, whereas locomotor activity and novel objective recognition were largely preserved. In acute brain slice preparation, *SYT1*-D366E overexpression increased the frequency of spontaneous excitatory postsynaptic current

(sEPSC) and reduced electrically evoked EPSC amplitudes in hippocampal CA1 pyramidal neurons. High frequency optical stimulation of CA3-CA1 synapses, which expressed ChR2 via injection of AAV9-ChR2-mCherry into the CA3 region, elicited diminished synaptic responses in *SYT1*-D366E overexpressing mice compared with control vector-expressing mice. Finally, application of 4-aminopyridine (4-AP) prolonged evoked EPSC duration and partially enhanced synaptic responses in *SYT1*-D366E-overexpressing mice. These findings confirm that *SYT1*-D366E overexpression disrupts synaptic function and produces autistic behaviors. This AAV-mediated *SYT1*-D366E mouse model provides a valuable platform for investigating synaptic mechanism underlying *SYT1*-NDD and for evaluating therapeutic strategies restoring synaptic function and behavioral outcomes.

Disclosures: X. Guo: None. **Z. Wang:** None. **A. Rajooldezfuly:** None. **A. Safaei:** None. **B. Yu:** None. **J. Zhou:** None. **H. Nishimune:** None. **D. Li:** None. **D. Arnold:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.09/D9

Topic: A.06. Developmental Disorders

Support: AAP-2023-EIMA-332751

Title: Advanced behavioural phenotyping of the neurodevelopmental disorders induced by transgenerational exposure to anti-epileptic medication

Authors: *X. LEINEKUGEL[1], H. ROUAULT[2];
[1]INMED, INSERM U1249, Marseille Cedex 09, France; [2]Aix-Marseille Université, Univ. de Toulon, CNRS, CPT UMR 7332, Turing Ctr. for Living systems, Marseille, France, Ashburn, VA

Abstract: Clinical observations have established the high incidence of neurodevelopmental disorders, and in particular Autism Spectrum Disorders (ASDs), in children born from epileptic mothers treated with VPA during pregnancy. Investigations in animal models with prenatal exposure to VPA through injections in pregnant rats and mice have reproduced several key aspects of ASD behavioural phenotype. However, most of these investigations have used classical behavioural tests that have proven very efficient for the screening of psychoactive molecules, but which also showed clear limitations in terms of animal phenotyping. For instance, our recent investigations have highlighted the importance of aversion to novelty in fmr1-KO mice, an established genetic model of ASD, resulting in a major emotional disturbance for the animals during the first sessions in a novel environment, with a very likely incidence on their social or cognitive abilities.
We describe here mouse behavioural characterisation using video recordings combined with a non-invasive open-field platform resting on ultra-sensitive sensors capable of detecting the

slightest movements of the animal (down to individual heartbeats in a mouse), thus capturing the signatures of a set of behaviours of interest (tremor, stereotypies, etc.) that remain inaccessible to existing systems. Using a computational neuro-ethological approach, including machine learning algorithms, we now report on the behavioural phenotypes expressed in these transgenerational neurodevelopmental disorders induced by the exposure to VPA, including emotional and attentional components that are often overlooked.

Disclosures: X. Leinekugel: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); share holder and consultant for Roddata SAS. **H. Rouault:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.10/D10

Topic: A.06. Developmental Disorders

Support: SFARI (AN-AR-Pilot Progression-00009493)
NICHD (R21 HD119466)
NICHD (R01 HD092593-01)

Title: Too Much of a Good Thing: excess prenatal allopregnanolone exposure disrupts neurobehavioral development in mice

Authors: *S. NENCINI, C.-M. VACHER, A. A. PENN;
Pediatrics, Columbia Univ., New York, NY

Abstract: Allopregnanolone (ALLO) is a placental neuroactive steroid that positively modulates GABA_A receptor signaling and supports late-gestation brain development. The cerebellum is increasingly implicated in autism spectrum disorder (ASD). We previously showed that placental ALLO insufficiency in a Cre-lox placental conditional knockout model (plKO; *Akr1c14* deletion in Cyp19a-Cre(+) trophoblasts) disrupts cerebellar development and produces ASD-like phenotypes in male offspring, including reduced sociability and increased stereotypies (Vacher et al., *Nat Neurosci*, 2021). Normalizing ALLO during gestation rescued these outcomes, while elevating ALLO in control (Cre(-)) littermates suggested that excessive exposure also altered neurodevelopment. These findings support an optimal "dose window" for ALLO signaling *in utero*. Here, we tested whether transient ALLO excess is sufficient to induce ASD-like behaviors in wild-type (WT) C57BL/6J mice. Pregnant dams received a single intraperitoneal injection of ALLO (10 mg/kg) at embryonic day (E) 15.5, a developmental stage characterized by high endogenous placental ALLO production. Offspring were evaluated from juvenile development through early adulthood (postnatal day 30) using a behavioral battery assessing social interaction and motor repetitive/stereotyped behaviors. Outcomes were compared with vehicle-treated WT mice and interpreted relative to established plKO (Cre(+)) and control (Cre(-)) phenotypes.

Prenatal ALLO exposure did not reduce social preference in WT offspring, but increased stereotyped behaviors (notably gnawing) and impaired motor performance. These results indicate that both insufficient and excessive prenatal ALLO exposure can produce enduring yet distinct, domain-specific ASD-like behavioral changes. These findings support a critical role for placental ALLO signaling in neurodevelopment and motivate ongoing studies examining cerebellar white-matter organization, Purkinje cell development, neuroinflammatory responses, and GABA_A receptor signaling to clarify how placental endocrine dysregulation contributes to ASD-relevant risk.

Disclosures: S. Nencini: None. **C. Vacher:** None. **A.A. Penn:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.11/D11

Topic: A.06. Developmental Disorders

Support: Princeton University Accelerator Grant
BlinkLab Limited

Title: Multivariate Neurobehavioral Measures as Objective Markers of Autism

Authors: *K. D. GULTIG[1,4], P. BOELE[2,4], L. ROGGEVEEN[4], E. SOONG[3,4], H.-J. BOELE[5,3,4]; [1]Neurosci., Erasmus Univ. Med. Ctr., Amsterdam, Netherlands; [2]Neurosci., [3]Erasmus Univ. Med. Ctr., Rotterdam, Netherlands; [4]BlinkLab Limited, Perth, Australia; [5]Neurosci., Princeton Neurosci. Inst., Princeton, NJ

Abstract: Autism diagnostic evaluations currently rely heavily on subjective measures such as caregiver or clinician observations. Computer-vision based analysis of neurobehavioral responses offers a potential objective tool to complement existing evaluations. These analyses may include structured assessments of well-studied neurophysiological mechanisms, such as habituation and prepulse inhibition of the acoustically evoked eyelid startle reflex as well as broader measures of spontaneous sensorimotor behavior, including postural control, head and hand movements and vocalizations. Using smartphone-based measurements of structured and spontaneous neurobehavioral responses, we found distinct differences between neurotypical and autistic children in a cohort of 431 individuals. These measurements were reliably captured in real-world clinical environments highlighting their potential value as a scalable tool, particularly important for low-resource settings. Given the heterogeneity of the autism phenotype, these group-level differences were not sufficient to support individual level prediction across multiple population groups. Thus, we evaluated the predictive performance of a machine-learning model trained on multivariate neurobehavioral measurements to classify clinical autism diagnoses and achieved an accuracy of 80% in an independent holdout set. These results provide preliminary evidence for an objective, standardized tool to add to existing autism evaluations. We are now

expanding these findings to examine their generalizability across diverse populations and cultural contexts.

Disclosures: K.D. Gultig: A. Employment/Salary (full or part-time):; BlinkLab Limited, Perth, Australia. **P. Boele:** A. Employment/Salary (full or part-time):; BlinkLab Limited, Perth, Australia. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlinkLab Limited, Perth, Australia. **L. Roggeveen:** A. Employment/Salary (full or part-time):; BlinkLab Limited, Perth, Australia. **E. Soong:** A. Employment/Salary (full or part-time):; BlinkLab Limited, Perth, Australia. **H. Boele:** A. Employment/Salary (full or part-time):; BlinkLab Limited, Perth, Australia. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlinkLab Limited, Perth, Australia.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.12/D12

Topic: A.06. Developmental Disorders

Support: The Society for the Study of ASD and Social-Communication (SSAS-C)

Title: Cognitive-Kinesthetic training reveals reciprocal foveal-peripheral reorganization of visual cortex in autism

Authors: *L. LIKOVA[1], C. W. TYLER[2], M. LIANG[3];
[2]Smith-Kettlewell Brain Imaging Ctr., [3]Res., [1]Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: INTRODUCTION. The Cognitive-Kinesthetic (C-K) Training method is a memory-based active-learning paradigm that uses drawing-from-memory to engage perception, cognition, and action within a unified functional loop. Across blind and sighted populations, C-K training has produced robust transfer-of-learning effects and large-scale reorganization of brain function and connectivity, offering strong therapeutic potential. Autism Spectrum Disorder (ASD) is characterized by atypical connectivity and altered organization across multiple large-scale cortical networks. By simultaneously engaging perceptual, cognitive, and behavioral processes, C-K training may promote adaptive network reorganization in ASD. METHODS. In a case study of ASD, five 2-hour sessions of C-K Memory-Drawing Training (Likova, 2012) were completed. Whole-brain fMRI (Siemens 3T Prisma) was acquired pre- and post-training during visual and blindfolded-haptic memory encoding (30 s) and memory drawing (30 s) of raised-line images, repeated three times per image and modality. RESULTS. Memory drawing, both visual and blindfolded-haptic, engaged substantially more extensive cortical networks than memory encoding. Following training, activation increased markedly in frontal, parietal, and temporal cortices, including regions supporting attention, memory, and executive control. The most

striking effect emerged in visual cortex. Prior to training, blindfolded-haptic memory drawing strongly suppressed primary visual cortex (V1). Post-training, the same non-visual task elicited robust V1 activation. This activation was confined to mid- and peripheral-field representations, whereas foveal representations remained suppressed. Remarkably, this pattern was reciprocal to that observed during visual memory drawing, which *activated* foveal V1 while *suppressing* peripheral representations. A similar modality-specific organization was observed in lateral occipital cortex, where haptic drawing preferentially engaged peripheral retinotopic representations and higher-order visual areas. CONCLUSIONS. These findings demonstrate that brief C-K training can induce large-scale cortical reorganization in ASD, and reveal a previously unreported reciprocal foveal-peripheral organization of visual cortex during visual and non-visual memory-guided tasks. The results provide new insight into the functional architecture and suggest substantial latent plasticity of visual and cognitive networks. They identify C-K training as a promising approach for driving adaptive reorganization in autism.

Disclosures: L. Likova: None. **C.W. Tyler:** None. **M. Liang:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.13/Web Only

Topic: A.06. Developmental Disorders

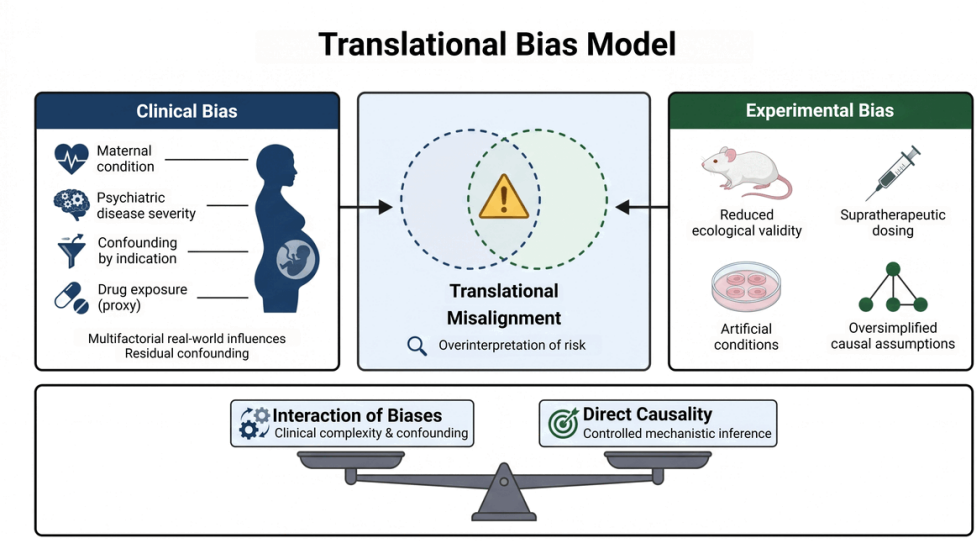
Support: CAPES Brazil

Title: Quantifying clinical-experimental divergence in prenatal pharmacological exposure and ASD risk: The Translational Bias Model

Authors: *B. A. CHICHARO[1], L. MOTA DA SILVA[2];
[1]Neurosci. Postgraduate Program, [2]Lab. of Pharmacol. Applied to the Gastrointestinal Tract and its Interactions, Federal Univ. of Santa Catarina, Florianópolis, Brazil

Abstract: The current gap between clinical and experimental evidence regarding prenatal drug exposure and the risk of Autism Spectrum Disorder (ASD) remains a critical challenge for establishing causality in neurodevelopmental research. To quantify this divergence and investigate its structural determinants, a quantitative synthesis of 81 studies (54 clinical, 27 experimental) across 10 pharmacological classes was performed. Following PRISMA 2020 guidelines (PROSPERO: CRD420261360514), searches were conducted in PubMed/MEDLINE, Embase, Scopus, and Web of Science through February 2026. Bias risk was evaluated using the Newcastle-Ottawa Scale (NOS) for clinical studies and the SYRCLE tool for experimental studies. The certainty of evidence was assessed with the GRADE method. For most classes, the evidence was rated as very low certainty. The analysis revealed a systematic divergence: clinical findings were often attenuated after adjusting for confounding, while experimental models consistently reported ASD-like phenotypes, most notably for antidepressants, with 22

experimental-positive findings versus predominantly attenuated or null clinical associations. Preclinical studies frequently used supratherapeutic doses, limited ecological validity, and did not analyze sex-specific effects. To explain this persistent divergence, we developed the Translational Bias Model, which conceptualizes how interacting sources of bias may amplify this divergence and promote overinterpretation of pharmacological risk. These results emphasize the importance of methodologically rigorous approaches to improve causal inference and support clinical decision-making.



Disclosures: B.A. Chicharo: None. **L. Mota da Silva:** None.

Poster

PSTR340: Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.14/D13

Topic: A.06. Developmental Disorders

Support: JST Moonshot Grant JPMJMS2292
AMED Grant JP1271303
JSPS KAKENHI Grant JP 24K16067
JSPS KAKENHI Grant JP 26K00007

Title: EEG Complexity in Adults with Autism Spectrum Disorder: Context-Independent Reduction and Attenuated Reactivity to Social Stimuli

Authors: *T. NAOE[1,2], Y. SHIKAUCHI[2], T. ITAHASHI[2], K. TANAKA[3], T. OKIMURA[2], R.-I. HASHIMOTO[4,2], H. OHTA[2], Y. SATO[3], M. NAKAMURA[2];
[2]Med. Inst. of Developmental Disabilities Res., [3]Brain Function Analysis & Digital Med. Res. Inst., [1]Showa Med. Univ., Tokyo, Japan; [4]Tokyo Metropolitan Univ., Tokyo, Japan

Abstract: Brain function emerges from temporal dynamics, and an appropriate level of neural complexity is thought to support flexible information processing. Electroencephalographic (EEG) studies using multiscale entropy (MSE), a measure of physiological complexity across multiple temporal scales, have reported reduced neural complexity at longer temporal scales in individuals with autism spectrum disorder (ASD). However, most evidence to date comes from infant and child samples, leaving adult data scarce and the relationships among reduced MSE, clinical symptoms, and cognitive processing insufficiently understood. We analyzed EEG from adults with ASD (n = 39 [13 female], mean age: 35.82 ± 10.72 years) and typically developing controls (TD; n = 42 [10 female], mean age: 36.45 ± 12.49 years) at rest and while viewing Inscapes and Partly Cloudy, which served as non-social and social movie stimuli, respectively. We examined group differences in MSE and its modulation across experimental conditions, as well as during cognitive-affective events in the social movie. We also examined associations between this modulation and clinical symptom severity, assessed using the Autism Diagnostic Observation Schedule-2 (ADOS-2). Across experimental conditions, adults with ASD showed lower MSE at longer time scales than TD adults (EEG signals sampled at 22.22-6.67 Hz, Hedges' g = -0.439 to -0.974, cluster-level p = 0.003). Partly Cloudy is a short animated film with well-characterized time windows that engage mentalizing and empathic pain-related networks. We therefore compared EEG MSE during these identified time windows with EEG MSE during the non-social condition (Inscapes). Adults with ASD did not show the mentalizing-related increase in long-scale MSE (rank-biserial r = 0.249, FDR-corrected p = 0.176) that was observed in TD adults (rank-biserial r = 0.502, FDR-corrected p = 0.005). Among participants with ASD, empathic pain-related increases in long-scale MSE were weaker in those with higher ADOS-2 Social Affect scores (ρ = -0.347, FDR-corrected p = 0.047). These findings suggest that reduced long-scale MSE is a robust neurophysiological feature of ASD in adulthood. In addition, attenuated MSE modulation during social-cognitive processing may reflect atypical neural dynamics relevant to social information processing and social communication differences.

Disclosures: T. Naoe: None. **Y. Shikauchi:** None. **T. Itahashi:** None. **K. Tanaka:** None. **T. Okimura:** None. **R. Hashimoto:** None. **H. Ohta:** None. **Y. Sato:** None. **M. Nakamura:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.01/D14

Topic: A.06. Developmental Disorders

Support: Simon's Foundation for Autism Research

Title: Development of primary somatosensory cortex in Fmr1 knockout rats

Authors: *M. REID, J. C. DOOLEY;
Biol. Sci., Purdue Univ., West Lafayette, IN

Abstract: Children with neurodevelopmental disorders, including autism, frequently present with sensorimotor deficits and poor sleep. During infancy, sensorimotor circuits are refined alongside a background of increased neural plasticity and sleep, with infants spending the majority of their time in rapid eye movement (REM) sleep. However, the precise mechanisms that link early sleep disruptions to altered sensory processing in autism remain unclear. To investigate these mechanisms, we can look to Fragile X Syndrome (FXS), the most common genetic driver of autism. This study aims to characterize differences in sleep and primary somatosensory cortex (S1) activity in *Fmr1* knockout rats compared to wild-type controls. Using *in vivo* extracellular electrophysiology, we recorded neural activity from wild-type and *Fmr1* knockout male rats on postnatal day 16 as they cycled between sleep and wake. Our preliminary findings suggest that Fmr1 knockouts exhibit less REM sleep and shorter REM sleep bout duration compared to controls, similar to what has been observed in humans. Ongoing investigations are exploring differences in movement-related activity in S1, as well as in the production and patterning of self-generated movements during sleep. Altogether, these findings offer important insights into early cortical development and sleep architecture in autism.

Disclosures: M. Reid: None. **J.C. Dooley:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.02/D15

Topic: A.06. Developmental Disorders

Support: NIH Grant R15 NS088776
St. Mary's College of Maryland

Title: Fmr1 deletion and early-life stress interact to increase cell proliferation and glial populations at the expense of immature neurons in the adult dentate gyrus

Authors: J. E. OMINUTA[1], L. E. SMITHA[1], K. J. BLANDIN[2], J. N. LUGO, Jr.[2], *S. E. LATCHNEY[1];
[1]St. Mary's Col. of Maryland, Saint Mary's City, MD; [2]Psychology and Neurosci., Baylor Univ., Waco, TX

Abstract: Fragile X Syndrome (FXS) is an inherited cause of intellectual disability and autism, arising from silencing of the *Fmr1* gene and loss of Fragile X Messenger Ribonucleoprotein 1 (FMRP). FMRP is an RNA-binding protein critically involved in neurodevelopmental processes, including neurogenesis. We examined the proliferation and maturation of adult-born dentate

granule cells (abDGCs) and glial populations in *Fmr1* knockout (KO) and wild-type (WT) mice at 4, 12, and 24 weeks of age under control and early-life stress (ELS) conditions. Based on prior findings, we hypothesized that KO mice would exhibit increased neurogenesis and atypical responses to ELS compared with WT mice. Using immunohistochemistry, we quantified multiple stages of neurogenesis in the dentate gyrus, including proliferating (Ki67+), immature (doublecortin [DCX]+), and apoptotic (cleaved caspase-3 [CC3]+) cells. We also assessed glia using Iba1 (microglia) and GFAP (astrocytes) immunoreactivity. KO mice displayed significantly increased Ki67+ proliferating and reduced CC3+ apoptotic cells across ages, accompanied by increased Iba1+ and GFAP+ glial densities. However, KO mice exhibited fewer DCX+ neuroblasts at later time points. When reared in ELS conditions, KO mice show blunted or no changes in neurogenesis and glial populations relative to WT mice reared in ELS conditions or KO mice in control conditions. These results indicate that FMRP loss disrupts hippocampal neurogenesis by increasing cell proliferation while limiting neuronal maturation and expanding glial populations. Moreover, the absence of neurogenic and glial responses to ELS in KO mice highlights a gene-environment interaction that may influence FXS-related neuropathology by limiting the adaptive capacity of the hippocampal neurogenic niche.

Disclosures: J.E. Ominuta: None. **L.E. Smitha:** None. **K.J. Blandin:** None. **J.N. Lugo:** None. **S.E. Latchney:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.03/D16

Topic: A.06. Developmental Disorders

Support: NIMH Grant R01MH116500

Title: Circuit dysregulation in Secondary Motor Cortex-Orbitofrontal Area during behavior in Fragile X mouse model

Authors: *M. YIN[1], V. SALDARRIAGA[2], A. A. CHUBYKIN[3];
[1]Weldon Sch. of Biomed. Engin., [3]Biol. Sci., [2]Purdue Univ., West Lafayette, IN

Abstract: Fragile X syndrome (FX), the most common inherited form of autism, is associated with behavioral hyperactivity combined with learning and memory deficits in perceptual decision-making tasks. Considering that these complicated tasks involve processing sensory input, evaluating sensory information, and producing motor actions, the neural circuit mechanism underlying these deficits remains unclear. We trained Fmr1 knockout (FX) and WT control mice on a visual Go/No-Go discrimination task. FX shows hyperexcitability during the task as they exhibit a higher licking rate. We then performed acute Neuropixels recordings in secondary Motor Cortex (MOs) and Orbitofrontal Area (ORB) simultaneously. During the task, both brain regions show activity in response to the visual cue and reward in a combined manner

of stimulus and behavioral outcome. We observed FX illustrate enhanced cue-related responses in both ORB and MOs. Additionally, reward-related MOs activity alters differently according to the behavioral outcome. Cluster-based analyses revealed disrupted neuronal response patterns, characterized by altered amplitude, latency, duration, and reduced stimulus discrimination. Together, these findings implicate overexcited ORB activity and dysregulated MOs processing consistent with FX behavioral impairments, which may help to provide a comprehensive understanding of the mechanistic changes in Fmr1 KO mice during decision-making and executive control processes. And will potentially shape a therapeutic avenue to rescue the Fragile X phenotype by targeting specific brain regions.

Disclosures: M. Yin: None. **V. Saldarriaga:** None. **A.A. Chubykin:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.04/D17

Topic: A.06. Developmental Disorders

Support: NIH R01NS137084
AR230041

Title: Role of locus coeruleus in sleep impairments in Fragile X syndrome

Authors: *N. SANKAR[1], A. ANDING[2], C. HUNTINGTON[1], Y. CABRERA[3], V. KOTA[3], P. ZHONG[3], A. DUNAEVSKY[3];
[1]Dept. of Pharmacol. and Exptl. Neurosci., [2]Dept. of Genetics, Cell Biol. & Anat., [3]Dept. of Neurolog. Sci., Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Fragile X syndrome (FXS) is a neurodevelopmental disorder characterized by learning difficulties and other behavioral impairments including sleep disturbances. However, the mechanism underlying sleep deficits in FXS is vastly understudied. Our lab has observed reduced and fragmented sleep (non-rapid eye movement, NREM) in the *Fmr1* KO mouse model of *FXS*. An increase in wake-like intrusions during NREM called microarousals in *Fmr1* KO mice contributes to NREM fragmentation. Locus coeruleus (LC) acts as a primary source of norepinephrine (NE) in the brain and is important for regulating sleep microarchitecture. Importantly, LC can control occurrences of microarousals. Thus, we hypothesized that abnormal LC activity underlies sleep disturbances in FXS. To examine LC activity during different sleep stages, two-months old *Fmr1* KO/dopamine beta-hydroxylase (Dbh)-Cre and wild-type littermates were injected with AAV to express the calcium indicator jGCaMP8 in LC neurons and implanted with optical fiber and electroencephalogram/electromyogram (EEG/EMG) devices, for simultaneous fiber photometry and EEG/EMG recordings. To investigate NE activity in one of the LC projection areas, mice were injected with NE sensor ($GRAB_{NE}$) in the medial prefrontal cortex (mPFC) and similar fiber photometry and EEG/EMG recordings were

obtained. LC's role in homeostatic sleep was examined by sleep depriving (SD) EEG/EMG-implanted TRAP/Ai14/*Fmr1* KO and wildtype animals for 5 hours following 4-hydroxytamoxifen (4OHT) injection to label active cells in LC. Animals in restoration group were injected with 4OHT following deprivation and were allowed to recover from deprivation. Sleep architecture and homeostasis were evaluated by EEG/EMG recordings. Our preliminary results show that LC-NE activity is higher during wakefulness and microarousal, reduced during NREM and mostly silent during REM sleep. There is a trend for increased NE peak value during MA ($p=0.078$, $n=5$-7) in *Fmr1* KO animals. Additionally, LC in *Fmr1* KO SD group shows higher number of active cells (labelled as tdTomato) compared to wild-type ($p=0.0006$, $n=4$). Overall, these results indicate that LC hyperactivity might contribute to impaired sleep in FXS.

Disclosures: N. Sankar: None. **A. Anding:** None. **C. Huntington:** None. **Y. Cabrera:** None. **V. Kota:** None. **P. Zhong:** None. **A. Dunaevsky:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.05/D18

Topic: A.06. Developmental Disorders

Support: Office of the Assistant Secretary of Defense for Health Affairs through the Autism Research Program under Award No. (HT9425-23-1-0395)

Title: Developmental comparison of auditory brainstem response in two genetically-distinct models of autism spectrum disorder

Authors: *H. WANG[1], M. INAMDAR[3], B. D. AUERBACH[2];
[1]Neurosci., Univ. of Illinois Urbana-Champaign, Champaign, IL; [2]Mol. & Integrative Physiol., Univ. of Illinois Urbana-Champaign, URBANA, IL; [3]Univ. of Illinois Urbana Champaign, Urbana, IL

Abstract: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition defined by impairments in communication, sensory processing, and social interaction, and this heterogeneity has impeded diagnosis and treatment. ASD has a strong but complex genetic basis, with hundreds of implicated risk genes, many converging on shared cellular and molecular pathways and suggesting biologically distinct subtypes. Yet the genotype-to-phenotype relationship remains intricate: Fragile X syndrome (FXS) and tuberous sclerosis complex (TSC), two leading single-gene causes of ASD, act through a shared molecular pathway but produce opposing changes at the synaptic and cellular level despite overlapping behavioral phenotypes. ASD is also a developmental disorder, so useful biomarkers must capture atypical developmental trajectories rather than static endpoints. This points to a key gap: the need for objective, translational biomarkers measurable across development and robust across ASD of distinct etiology. Auditory processing is a promising target, as over 70% of autistic individuals report

auditory hypersensitivity and sound-processing difficulties. The auditory brainstem response (ABR) is well suited to this role: it is fast, non-invasive, routinely used in children, including newborns, and captures sound-evoked activity across multiple levels of the auditory pathway, giving it high translational value as an early biomarker of autism risk. Prolonged ABR latencies have been reported in autistic individuals, but their developmental time course is unclear, and little is known about whether ABR signatures differ across genetically distinct forms of ASD. To address this, we measured ABRs across development (from ear opening to adulthood) in Fmr1 KO and Tsc2 rat models of FXS and TSC, which we have previously shown to exhibit atypical sound processing in adulthood. We found atypical but distinct developmental trajectories in the two models. These results indicate that while ABR is a valuable translational tool for detecting early auditory alterations in ASD, the divergent trajectories of FXS and TSC caution that a single ABR signature is unlikely to generalize across etiologies; sensitive early biomarkers will need to account for subtype-specific developmental differences.

Disclosures: H. Wang: None. **M. Inamdar:** None. **B.D. Auerbach:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.06/D19

Topic: A.06. Developmental Disorders

Support: NIH Grant 1P50HD118717-01
NIH Grant U54HD104461

Title: Resting-State EEG Biomarkers in Fragile X Syndrome: Relationships with FMRP Protein Levels & Diagnostic Group

Authors: *E. E. MCCORD[1], G. WESTERKAMP[2], S. PILOTO[1], E. SMITH[1], E. V. PEDAPATI[3], C. ERICKSON[1];
[1]Div. of Child and Adolescent Psychiatry, [2]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [3]Psychiatry, Cincinnati Children's Hosp. Med. Ctr., Cnicinnati, OH

Abstract: Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and the leading monogenic cause of autism spectrum disorder (ASD). FXS emerges from transcriptional silencing of the *FMR1* gene and subsequent loss of Fragile X Messenger Ribonucleoprotein (FMRP), which disrupts synaptic plasticity and cortical excitation/inhibition (E/I) balance, among other neurodevelopmental phenomena. Prior work in our lab has identified significant correlations between FMRP expression and Deviation IQ in males and females with FXS, motivating our ongoing interest in relating FMRP as a biological variable to neurophysiological, behavioral, and clinical metrics. Electroencephalography (EEG) offers a sensitive, non-invasive window into FXS-related neurophysiology. However, the quantitative relationship between FMRP protein levels and resting-state EEG biomarkers, across the full

developmental spectrum, has not been systematically characterized using modern spectral decomposition methods. Here, we analyzed resting-state EEG recordings from 165 individuals with FXS (113 male, 52 female; age 0.8-57.4 years) and 118 age/sex-matched typically developing controls (TDC) (83 male, 35 female) to 1. characterize resting-state EEG aperiodic and periodic spectral features in FXS and 2. examine how these features relate to FMRP concentration across sex, FMRP expression group (Zero, Trace, Low, Moderate), and developmental stage (pediatric, adolescent, adult). Our work aims to not only provide further clarity into how FXS molecular phenomena informs brain activity, but to also establish a foundation for integrating EEG measures as pharmacodynamic biomarkers in FXS research. In conjunction with novel therapeutics, these measures can be used to best mitigate the symptoms of cortical hyperexcitability and hypersensitivity in FXS.

Disclosures: E.E. McCord: None. **G. Westerkamp:** None. **E.V. Pedapati:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.07/D20

Topic: A.06. Developmental Disorders

Support: Randi J. Hagerman Summer Scholars Research Award - Tanvi Kamra
BBRF Young Investigator Grant - Dr. Nisha Raj

Title: Integrative multiomic analysis of postmortem brains from individuals with Fragile X Syndrome (FXS)

Authors: *T. KAMRA, N. RAJ;
Dept. of Human Genet., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Fragile X Syndrome (FXS) is the most prevalent form of inherited intellectual disability and the leading monogenic cause of autism spectrum disorder. In healthy individuals, the 5′ untranslated region (UTR) of FMR1 contains a polymorphic CGG trinucleotide repeat, typically ranging from 5 to 44 copies. When this repeat expands beyond the normal threshold, it causes a spectrum of repeat-associated disorders. FXS is caused by the expansion of over 200 repeats leading to transcriptional silencing of the FMR1 gene that encodes for the RNA-binding protein Fragile X Messenger Ribonucleoprotein 1 (FMRP), which plays a prominent role in the regulation of synaptic function, neurodevelopment, and plasticity in post-synaptic neurons. The molecular consequences of altered FMRP expression in the human brain remain largely unexplored. Large-scale transcriptomics studies have been conducted to identify risk genes and networks in autism, schizophrenia, and other related NDDs, and these have been critical to help us better understand the biology of these disorders. However, there are far fewer studies that involve in-depth proteomic analyses in disease-relevant samples. Given that the relationship between transcription and translation is not strictly linear, and proteins are often the direct target

of therapeutics, it is important to validate these transcriptomic studies at the protein level. To address the historical lack of human-disease-relevant models for understanding patient mutations, the study uses primary human brain tissue to ensure disease relevance and translational impact by performing a comprehensive and integrative multiomic analysis of human postmortem brains from full mutation FXS individuals and age- and sex- matched neurotypical controls. Paired bulk RNA sequencing and quantitative proteomic analysis identified several differentially expressed genes (DEGs) and differentially abundant proteins (DAPs) within the full mutation condition. Gene ontology analysis of significantly downregulated proteins indicates enrichment of terms linked to cytoskeleton development and synaptic function within the full mutation. Our analyses also revealed several shared and distinct biological pathways in fragile X-associated disorders, including the full mutation and premutation, highlighting neuronal projection morphogenesis being significantly downregulated at the protein level. These findings in human patient tissue provide a new understanding of FXS pathology, which could inform therapeutic development.

Disclosures: T. Kamra: None. **N. Raj:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.08/D21

Topic: A.06. Developmental Disorders

Support: NIH Grant 4RF1MH106490-09

Title: Temporal and spatial expression of FMR1 isoforms in the developing human brain

Authors: *K. E. REYNOLDS[1], M. MAJID[1], K. KEUM[1], R. MCDERMOTT[1], O. LIN[2], K. HUANG[2], Y. YANG[1];
[1]Tufts Univ. Sch. of Med., Boston, MA; [2]Mol. Imaging Core, Dana-Farber Cancer Inst., Boston, MA

Abstract: EEncoded by the FMR1 gene, the FMRP protein is one of the most crucial RNA-binding proteins in the developing brain. Human FMR1 mRNA undergoes extensive alternative splicing of its 17 exons to produce over 20 unique protein-coding isoforms. Surprisingly, the temporal and spatial expression patterns of FMR1 isoforms in the developing human brain remain largely unknown. Furthermore, it is unclear whether alternative splicing of FMR1 confers isoform-specific functions; however, FMR1 exon 12 (E12) is alternatively spliced and encodes a variable loop region of the KH2 RNA-binding domain, suggesting its potential influence on RNA binding. We therefore aimed to better understand FMR1 isoform expression patterns in human tissue to address this gap in our knowledge, with a particular focus on FMR1 E12 as it is the only alternatively spliced region within a known RNA-binding domain. We first analyzed published RNA sequencing data to confirm that FMR1 E12+ isoforms were expressed in human

cortex and hippocampus. Developmental sequencing analysis was challenging due to the scarcity of juvenile human data, so we designed E12-specific and total FMR1 primers to quantify relative expression of E12+ isoforms throughout postnatal development using qPCR. In human dorsolateral prefrontal cortex (age 4-35, both sexes), FMR1 E12+ comprised ~15% of total FMR1 RNA prior to age 10 but only ~5% of total FMR1 by adulthood, indicating developmental downregulation of E12+ isoforms, a trend that was conserved in mouse. To further understand the spatial expression patterns of FMR1 isoforms, we designed Xenium spatial transcriptomics probes to detect alternative splicing in exon 12, as well as exons 15 and 17. This analysis revealed that E12 was retained in ~30% of FMR1 isoforms in the hippocampus (age 13-19), and was present in both hippocampal and cortical neurons and astrocytes. We also developed a novel E12+ FMRP antibody, allowing us to detect FMRP E12+ protein in both neurons and astrocytes. Further, FMRP E12+ immunoblotting revealed that the proportion of E12+ isoforms relative to total FMRP peaked during childhood (<age 10, both sexes) in human cortex and was developmentally downregulated, similar to FMR1 E12+ temporal expression. Finally, FMR1 E12+ was found to be positively correlated with FMRP levels in human leukocytes by reanalyzing previously published data, suggesting that FMR1 E12+ isoforms may drive FMRP protein expression. Together, these results provide the first temporal and spatial characterization of E12+ FMR1 and FMRP isoforms in the human cortex and hippocampus during postnatal development, and highlight the potential importance of FMR1 exon 12.

Disclosures: K.E. Reynolds: None. **M. Majid:** None. **K. Keum:** None. **R. McDermott:** None. **O. Lin:** None. **K. Huang:** None. **Y. Yang:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.09/D22

Topic: A.06. Developmental Disorders

Support: R21AG093546 (RS)
R01AG100834 (RS, JMM)
Nemours Programmatic Funding (RS, AH, MO):

Title: Auditory Stimulation recovers cognitive and behavioral deficits in Fmr1-ko mice.

Authors: *M. OUARDOUZ[1], A. E. HERNAN[2], M. MAHONEY[3], R. SCOTT[1];
[1]Nemours Children Hlth., Wilmington, DE; [2]Neurolog. Sci., Nemours Children's Health/University of Delaware, Wilmington, DE; [3]research, Jackson Labs., Bar Harbor, ME

Abstract: Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by a CGG trinucleotide repeat expansion in the *FMR1* gene, resulting in loss of Fragile X Messenger Ribonucleoprotein (FMRP) expression. FXS is characterized by intellectual disability, social deficits, repetitive behaviors, and a high prevalence of autism spectrum disorder. We have

previously shown that medial septal deep brain stimulation improves cognitive and behavioral deficits in Fmr1 knockout (Fmr1-KO) mice and restores hippocampal synaptic plasticity. Here, we investigated whether a non-invasive auditory stimulation paradigm could similarly ameliorate behavioral impairments in Fmr1-KO mice. Fmr1-KO mice were exposed to auditory stimulation (PD22-40) for 2 minutes, three times daily at one-hour intervals for 5 consecutive days. Behavioral assessments were performed at 2-3 months of age for novel object recognition, social interaction, and marble burying tests. Fmr1-KO mice exhibited significant social interaction deficits compared with wild-type controls ($p < 0.001$), whereas auditory stimulation restored social behavior to control levels. Recognition memory was impaired in Fmr1-KO mice relative to controls ($p = 0.003$) and was significantly improved following auditory stimulation. Fmr1-KO mice also displayed increased repetitive and compulsive-like behaviors, including enhanced marble burying and foraging activity ($p = 0.01$), which were normalized by auditory stimulation. These findings demonstrate that brief auditory stimulation is sufficient to improve cognitive, social, and repetitive behavioral abnormalities in Fmr1-KO mice. The results suggest that sensory-based neuromodulation may represent a promising non-invasive therapeutic strategy for alleviating behavioral deficits associated with Fragile X syndrome.

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

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.10/E1

Topic: A.06. Developmental Disorders

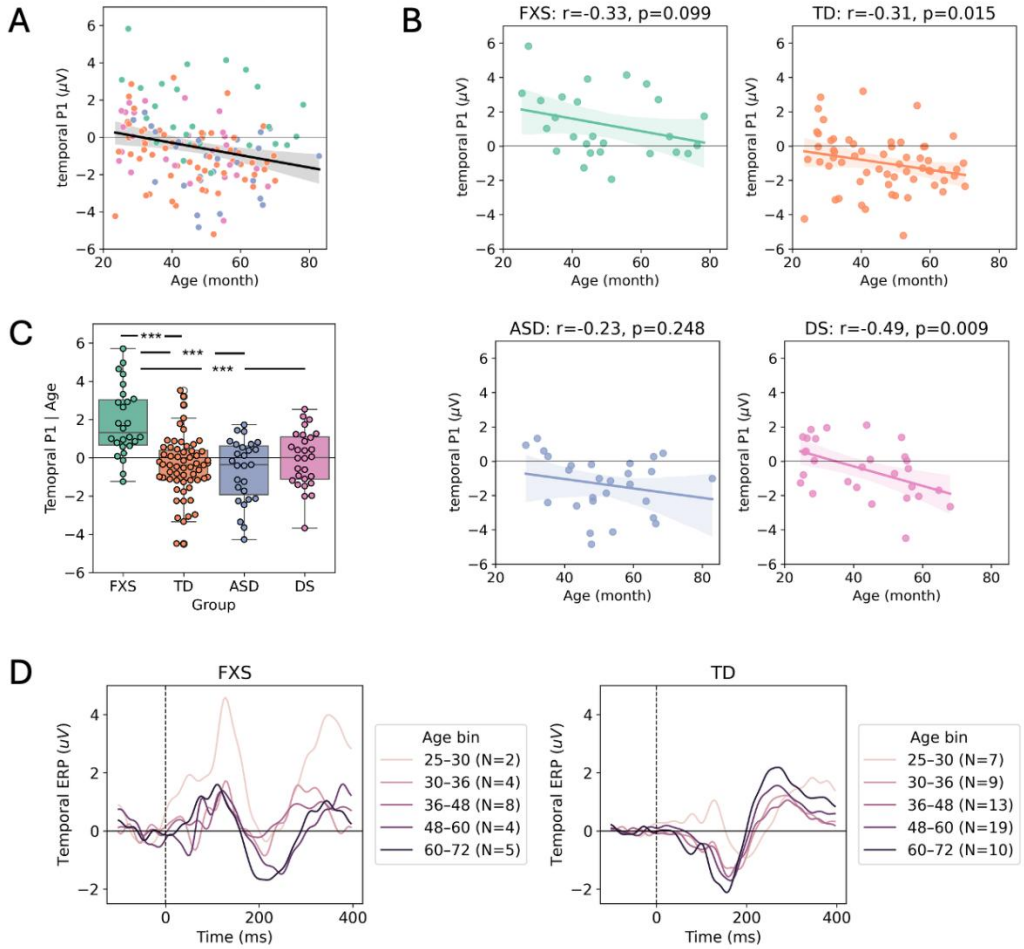
Support: NIDCD Grant K23DC017983
FRAXA Research Foundation
Autism Science Foundation
Pierce Family Foundation
Thrasher Research Fund

Title: Delayed maturation and altered habituation of auditory evoked potentials in children with Fragile X syndrome

Authors: *W. W. AN, M. KHELA, M. TSOU, C. L. WILKINSON;
Boston Children's Hosp., Boston, MA

Abstract: Fragile X syndrome (FXS) is a genetic disorder commonly associated with autism spectrum disorder (ASD) and intellectual disability (ID). Mouse models show altered auditory responses and habituation, but human auditory evoked potential (AEP) studies have reported mixed findings, limiting translation between preclinical and clinical research. This study aims to characterize AEPs across spatial locations and age in preschool-aged children with FXS and compare findings with ASD and Down syndrome (DS) to assess specificity. Children with FXS

(n=27), ASD (n=27), DS (n=28), and typical development (TD; n=60) completed an auditory habituation paradigm consisting of three repeated tones per trial. High-density EEG was analyzed using spatial principal component analysis to define frontal and temporal regions of interest. P1 amplitude was quantified for the first tone (STM1), and habituation was calculated as the STM1-STM3 difference. Linear regression models examined effects of age and diagnosis. In the frontal region, children with FXS showed significantly lower P1 amplitude than TD peers across the age range studied (all $p<0.038$), whereas ASD and DS did not differ from TD. Significant habituation was observed in TD ($p=0.002$) and ASD ($p=0.019$), but not in FXS ($p=0.889$) or DS ($p=0.503$). In the temporal region, P1 amplitude decreased with age across groups ($p<0.001$) (Figure 1A & B). However, FXS exhibited markedly elevated temporal P1 amplitude relative to all other groups (all $p<0.001$) (Figure 1C). Moreover, AEP waveforms in FXS across all age bins (25-78 months) were most strongly correlated with those of the youngest TD children (25-30 months; all $p<0.001$) (Figure 1D). Our findings in elevated temporal P1 amplitude and immature waveform morphology suggest delayed maturation of temporal auditory processing in FXS. Reduced frontal P1 amplitude and absent habituation indicate additional alterations in auditory neural function beyond delayed maturation alone. These findings were not observed in ASD or DS, suggesting that these AEP abnormalities may be specific to FXS.



Disclosures: W.W. An: None. **M. Khela:** None. **M. Tsou:** None. **C.L. Wilkinson:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.11/E2

Topic: A.06. Developmental Disorders

Support: GM113109

Title: Maintenance in object recognition memory following high frequency repetitive transcranial magnetic stimulation in aged Long-Evans rats

Authors: *B. PLAKKE[1], C. COLLINS[1], A. SPRINGER[1], T. MAJI[1], B. SIVAYOKAN[2], C. GEORGE[1], J. C. HERNANDEZ-PAVON[1];
[2]Psychological Sci., [1]Kansas State Univ., Manhattan, KS

Abstract: A decline in cognitive functioning is seen in aging, even in the absence of neurodegenerative disorders like Alzheimer's disease. This age-related decline in cognitive functioning does not have an abrupt onset in old age but can begin in middle age and progress with age. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that uses electromagnetic induction to modulate cortical excitability. In high-frequency rTMS (HF-rTMS) thousands of pulses are delivered at a frequency of 5-25 Hz leading to increased cortical excitability and synaptic plasticity. Therefore, HF-rTMS could be used to mitigate the decline in cognitive functioning brought on by aging. This project used male Long-Evans rats aged at least 12-months to study the effect of HF-rTMS on cognitive functioning. These rats were assigned to either the stimulation group or sham group and underwent stimulation/sham procedure over five consecutive days. Each day, the rats were anesthetized and head-fixed in a stereotax. A MagPro X100 stimulator equipped with a Cool-40 rat coil was used to administer HF-rTMS. The stimulation group received 1640 pulses at a frequency of 10 Hz and an intensity of 110% of resting motor threshold, divided into 41 trains of 40 pulses with an intertrain interval of 11 seconds. The sham group heard the clicks from the stimulator but did not receive any stimulation. All rats underwent the novel object recognition test before and after the TMS/sham procedure. During the sample phase of this test, rats explored two identical objects for 10 minutes. During the test phase, carried out 24 hours after the sample phase, they explored one object from the sample phase and one new object, and the time spent with each object was recorded. The stimulation/sham procedure and the pre-, post-tests were repeated after a minimum of 8 weeks. Results showed that rats from the stimulation and sham group started out with similar discrimination indices. Novel object discrimination improved significantly above chance among those in the stimulation group after the first set of HF-rTMS sessions (p = .006) and was maintained over time. However, in the sham group, the discrimination index further decreased over time such that the discrimination index was significantly lower in the sham group than the stimulation group before the second set of stimulation/sham session (p = .043). These findings

suggest that early HF-rTMS could help slow down the progression of age-related decline in cognitive functioning.

Disclosures: B. Plakke: None. **C. Collins:** None. **A. Springer:** None. **T. Maji:** None. **B. Sivayokan:** None. **C. George:** None. **J.C. Hernandez-Pavon:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.12/E3

Topic: A.06. Developmental Disorders

Support: R03MH133173

Title: Association of striatal dynorphin and enkephalin levels with restricted repetitive behavior in Fmr1 knockout rats

Authors: *B. SIVAYOKAN[1], B. PLAKKE[2];
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Abstract: Restricted repetitive patterns of behavior (RRBs) are characterized by repetition, rigidity, invariance, and inappropriateness. In infancy and childhood, RRBs are transient and characteristic of normal development. However, they often persist in neurodevelopmental disorders such as autism spectrum disorder and fragile X syndrome, and manifest as symptoms of neurodegenerative diseases. Although these behaviors are linked to dysfunctional striatal circuitry, changes in the striatal peptide neurotransmitters and their role in the emergence of RRBs in fragile X syndrome are not clearly defined. This study employed the Fmr1 knockout model of fragile X syndrome to assess repetitive behavior and its association with striatal neurotransmitters enkephalin and dynorphin. Male and female Fmr1 knockout (KO) and wildtype (WT) rats (at least 8 per group) from two age cohorts, postnatal day 40 and 12 months, underwent behavioral testing. During the open field test, whichwas conducted to assess RRBs, animals were placed in a clear plexiglass chamber and allowed to explore for 15 minutes on two consecutive days. Grooming test assessed repetitive grooming by applying two sprays of 10% sucrose solution on the dorsal coat of the animal to improve palatability and permit persistence of grooming. Following behavior testing, a subset of animals was euthanized, and their striatum was collected for quantification of dynorphin and enkephalin via enzyme-linked immunosorbent assays. All tests were carried out by blind-to-condition researchers. In general, increased RRBs were observed among KO animals than among WT animals with different forms of RRBs being prominent at each timepoint. While rearing was seen more among older rats, grooming and oral repetitive behavior were seen more among younger rats ($p < .001$ for all). KO males, irrespective of age, engaged in more oral repetitive behavior ($p = .029$), whereas KO females engaged more in rearing behavior ($p = .017$). While genotype-sex group differences in striatal dynorphin levels were not seen at either timepoint, striatal enkephalin levels were higher in WT females than KO

females (p = .024) and in WT males than KO males(p = .025) in the 12-month age cohort. These neurotransmitter levels were significantly associated with RRBs, such that RRBs increased significantly with increasing dynorphin to enkephalin ratio among older animals (p = .047), and with decreasing enkephalin levels in younger animals (p = .007). These findings suggest that striatal enkephalin and dynorphin signaling show age-related changes and could be involved in the emergence of RRBs in fragile X syndrome.

Disclosures: B. Sivayokan: None. **B. Plakke:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.13/E4

Topic: A.06. Developmental Disorders

Support: GM113109

Title: Cognitive and behavioral changes following low frequency repetitive transcranial magnetic stimulation in Fmr1 knockout rats

Authors: *C. COLLINS[1], A. SPRINGER[1], T. MAJI[1], B. SIVAYOKAN[2], C. GEORGE[1], J. C. HERNANDEZ-PAVON[1], B. PLAKKE[3];
[2]Psychological Sci., [3]Psychological Sciences, Behavioral Neurosci., [1]Kansas State Univ., Manhattan, KS

Abstract: Fragile X syndrome (FXS), an X-linked dominant disorder, is caused by a triplet repeat expansion in the FMR1 gene coding for fragile X messenger ribonucleoprotein (FMRP). FMRP is abundant in dendritic spines of neurons, where it plays a key role in regulating protein synthesis in the dendrite and synapses. The loss of FMRP in FXS results in immature dendritic spines and higher spine density, which leads to hyperexcitability and disrupted synaptic plasticity. Low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) is a non-invasive neuromodulatory approach that can reduce the hyperexcitability of neurons in FXS. This study explored the changes in behavior following LF-rTMS in the Fmr1 knockout rodent model of FXS. Male and female Fmr1 knockout (KO) and WT animals (stimulation and sham groups) aged 2-4 months underwent stimulation/sham procedure over five consecutive days. Each day, animals in both groups were anesthetized and head-fixed in a stereotax. The stimulation group received 500 TMS pulses at a frequency of 1Hz and an intensity of 110% of resting motor threshold using a MagPro X100 stimulator equipped with a Cool-40 rat coil. The sham group heard the clicks from the stimulator but did not receive any stimulation. Behavioral tests including novel object recognition, grooming, and nesting, were carried out before and after TMS/sham procedure by blind-to-condition researchers. In the novel object recognition test, animals explored two identical objects. After a delay of 10 minutes, one of these objects was replaced with a new object. The discrimination index in this test was significantly above chance

among KO rats in the stimulation group after LF-rTMS than pre stimulation (p = .010), indicating an improvement in short-term object recognition memory in this group. This was not seen among WT animals or KO animals in the sham group. In the grooming test, animals were sprayed with 10% sucrose solution to induce self-grooming. Results showed that the time spent grooming during the grooming test was not significantly different before and after stimulation/sham procedure. During the nesting test, animals were single-housed and given 6 nestlet squares. While the quality of the nest and the amount of nesting material shredded, both assessed 24 hours after nestlets were given, did not vary across time among the groups, the time spent interacting with the nestlets when they were first introduced significantly decreased after TMS in the KO stimulation group (p = .008), indicating a possible reduction in repetitive behavior. These findings suggest that LF-rTMS improves short-term object recognition memory and certain repetitive behavior in Fmr1 KO animals.

Disclosures: C. Collins: None. **A. Springer:** None. **T. Maji:** None. **B. Sivayokan:** None. **C. George:** None. **J.C. Hernandez-Pavon:** None. **B. Plakke:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.14/E5

Topic: A.06. Developmental Disorders

Support: GM113109

Title: Assessing social interaction and restricted repetitive behavior in young Fmr1 knockout rats

Authors: *J. GAY[1], B. SIVAYOKAN[2], B. PLAKKE[3];
[2]Psychological Sci., [3]Psychological Sciences, Behavioral Neurosci., [1]Kansas State Univ., Manhattan, KS

Abstract: Fragile X syndrome (FXS) is the most common single-gene cause of intellectual disability and a leading heritable cause of autism spectrum disorder. People with FXS can present with a range of cognitive deficits, restricted repetitive behavior, impaired social interaction, anxiety, and attention deficits, which all affect daily functioning. Similar deficits have also been demonstrated in *Fmr1* knockout (KO) rodents using a battery of different behavioral tests which are predominantly carried out outside the home cage. Here, a home cage-based behavioral experiment was designed to assess multiple behaviors including repetitive behavior such as digging, self-grooming, nestlet shredding, rearing, social interaction with cage mate, and interaction with novel objects introduced to the home cage. All *Fmr1* KO and wildtype rats (at least 07 per group) used in this ongoing project were bred in-house, and weaned, pair-housed with same sex litter mate, and genotyped at P21. At P40, several enrichment toys including a tunnel, wooden block, manzanita stick, and nestlet squares were introduced to the home cage and rat pairs were videotaped for 10 minutes. After 7 days, each rat was separated

from their cage mate and toys, placed in a clean cage with fresh bedding, and videotaped for 10 minutes. It was hypothesized that introduction to this new empty cage may trigger repetitive behaviors. Distance traveled and time spent rearing were scored using a custom automated program during the empty cage phase. Time spent digging was manually scored. All behavior testing and scoring were carried out by blind-to-condition researchers. Preliminary analyses show that while digging time was slightly greater in male KO rats and distance travelled was greater among female KO rats, these differences were not statistically significant. Social interaction was manually scored during the first 10 min task when objects were introduced. Preliminary analysis of these results show that female wildtype-wildtype pairs interact more with each other. Further analyses are ongoing to explore differences in object interaction and repetitive behaviors such as self-grooming.

Disclosures: J. Gay: None. **B. Sivayokan:** None. **B. Plakke:** None.

Poster

PSTR341: Fragile X Syndrome

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.15/E6

Topic: A.06. Developmental Disorders

Support: GM113109
R03MH133173

Title: Cognitive flexibility and gamma power in Fmr1 knockout rats

Authors: *T. MAJI[1], J. GAY[1], B. SIVAYOKAN[2], C. GEORGE[1], J. C. HERNANDEZ-PAVON[1], B. PLAKKE[3];
[2]Psychological Sci., [3]Psychological Sciences, Behavioral Neurosci., [1]Kansas State Univ., Manhattan, KS

Abstract: Fragile X syndrome (FXS) is an X-linked dominant disorder caused by a mutation in the FMR1 gene, which codes the protein FMRP. This protein, which is abundant in neuronal dendrites, is important for regulating synaptic plasticity. The loss of this protein in FXS leads to cognitive flexibility impairments. Loss of FMRP also leads to excitation/inhibition imbalance, which is reflected in electrophysiological recordings. This study explored cognitive flexibility and associated electrophysiological changes in aged Fmr1 KO and wildtype (WT) rats (at least 8 per group) rats using a touchscreen-based categorization task. After completing shaping procedures to touch the screen for food rewards, the rats were started on the categorization task, which used two categories of Gabor patches differing in frequency and orientation. The task consists of 80 trials in which 80 different exemplars, 40 from each category, are presented. Rats touch a pentagon displayed on the screen to initiate the trial. Then must press the cue and finally press left or right to make a correct choice. Eighty percent of all correct choices and twenty percent of all incorrect choices are rewarded. After 16 days of training on the initial

categorization rule, the rule was reversed. After 8 days on the reversed rule, a new rule based on different categories of Gabor patches was implemented. After the initial training, a subgroup of animals was implanted with a microarray electrodes in the prefrontal cortex. Following the post-surgical recovery period, these animals underwent the categorization task. All experiments were carried out by blind-to-condition researchers. Results showed that both KO and WT rats struggled to reach the criterion of 70% correct for each category. While the overall accuracy in the initial rule was similar for both KO and WT rats, the KO rats performed poorly when the rule was reversed ($p < .001$). Analysis of the local field potentials obtained from the implanted rats showed that high- and low-gamma power was greater in KO rats than WT rats ($p = .009$). Furthermore, gamma power decreased during the choice onset compared to cue onset among WT but not KO rats ($p < .001$). These findings suggest that while aged KO and WT rats struggle with cognitive flexibility, gamma power remains elevated only among Fmr1 KO rats.

Disclosures: T. Maji: None. **J. Gay:** None. **B. Sivayokan:** None. **C. George:** None. **J.C. Hernandez-Pavon:** None. **B. Plakke:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.01/E7

Topic: A.07. Development of Neural Systems

Support: NSTC 114-2314-B-006-081-MY2

Title: Gray Matter-Based Analysis of Preterm and Term Neonatal Brain Microstructure and Function in dHCP Dataset

Authors: *P. Y. HAN, S.-M. HUANG;
Dept. of Pharmacol., Natl. Cheng Kung Univ., Tainan City, Taiwan

Abstract: The human cerebral cortex undergoes rapid microstructural maturation during the neonatal period, encompassing synaptogenesis, dendritic arborization, and progressive gray matter elaboration with marked temporal and regional heterogeneity. Preterm birth, affecting approximately 10% of live births globally, disrupts these processes and is a leading cause of neurodevelopmental impairment, yet reliable early imaging biomarkers remain scarce. While diffusion MRI (dMRI) can non-invasively probe microstructural changes, prior studies have focused predominantly on white matter; whether distinct gray matter metrics predict outcomes across specific gestational windows remains unknown. Using Gray Matter-Based Spatial Statistics (GBSS) on dHCP data (n=660 infants, postmenstrual age 29.3-45.1 weeks), four skeletonized dMRI metrics were extracted across 32 cortical regions: fractional anisotropy (FA), mean diffusivity (MD), orientation dispersion index (ODI), and neurite density index (NDI). Sex was included as a covariate; sex-stratified analyses were not performed. Cross-sectional analysis confirmed robust developmental trajectories: MD decreased ($r=-0.865$) while NDI increased

(r=0.741), validating GBSS sensitivity to cortical maturation. Participants with complete assessments at 18-month follow-up (BSID-III, n=512; QCHAT, n=507; HINE, n=506) were stratified by scan age into seven groups. A metric relay effect was observed: NDI/FA dominated in early preterm (<34w), MD in late preterm (34-38w), and ODI in the peri-term window (38-40w), which is consistent with the dendritic arborization peak at this stage. Linear mixed models (covariates: gestational age at birth, scan age, sex; 442 family clusters to account for sibling and repeated-scan non-independence) identified significant associations ($q < .05$, FDR-corrected) with 18-month cognitive (NDI of STG post L: t=4.02; MD of STG middle L: t=3.39) and language scores (MD of cingulate anterior: t=3.99; MD of cingulate posterior: t=3.87). Higher cognitive/language performance was associated with higher MD in superior temporal gyrus and cingulate and lower NDI, suggesting a developmentally earlier but not deficient state in which relative microstructural looseness in temporal-limbic regions depicts a developmentally advantageous trajectory. No significant associations ($q < .05$, FDR-corrected) were found for motor, QCHAT, or HINE outcomes. These findings reveal gestational-age-specific windows in which dMRI metrics capture biologically distinct maturation processes, with peri-term cortical ODI serving as an exploratory candidate biomarker for future validation.

Disclosures: P.Y. Han: None. **S. Huang:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.02/E8

Topic: A.07. Development of Neural Systems

Support: Tetrad Initiative for Interdisciplinary Research, Michigan State University

Title: Influence of Early Environmental Exposures on DNA methylation and Brain Structural and Functional Development

Authors: *A. KAUR[1], H. SU[2], R. SADLER[3], Y. CUI[2], N. PANCHY[4], X. LIANG[5], R. C. KNICKMEYER[1];
[1]Inst. for Quantitative Hlth. Sci. and Engin., [2]Dept. of Statistics and Probability, Michigan State Univ., East Lansing, MI; [3]Michigan State Univ., Flint, MI; [4]Inst. for Cyber Enabled Res., [5]Dept. of Epidemiology and Biostatistics, Michigan State Univ., East Lansing, MI

Abstract: Background: Early life environmental stress can disrupt the development of stress-related brain regions, with long-lasting consequences for mental health. DNA methylation, including global genome-wide methylation levels, provides a key epigenetic mechanism through which environmental exposures shape gene expression and neural function. Understanding these processes may reveal early markers of risk and resilience.
Methods: This longitudinal study examined associations between census-tract-level population density and a composite index of neighborhood distress (z-scored poverty, lone parenthood, low

educational attainment, and unemployment) with brain structural and functional phenotypes, global DNA methylation and epigenetic aging. Outcomes were assessed at two time-points: 0-3 months (time-point 1) and 11-15 months (time-point 2), with functional connectivity available only at time-point 1. Subcortical volumes of stress- and reward-related regions (bilateral amygdala, hippocampus, caudate, putamen, pallidum, accumbens, and thalamus) and functional connectivity (within and between-network) of the amygdala, hippocampus, default-mode-network, and anterior insula, along with network metrics, were examined. Linear regression models adjusted for sex, maternal ethnicity, education, income, age at MRI/DNA collection, as appropriate. Multiple comparisons were controlled using the false discovery rate procedure. Results: Higher population density was associated with larger left caudate ($\beta = 0.638$, SE = 0.177; t (35) = 3.60, p_adj = 0.013) and right caudate volumes ($\beta = 0.635$, SE = 0.182; t (35) = 3.48, p_adj = 0.018). An interaction between distress and population density was associated with global DNA methylation ($\beta = 0.252$, SE = 0.00014; t (107) = 2.31, p_val = 0.022), whereas no significant association was observed with epigenetic aging. Global DNA methylation and epigenetic aging were not significantly associated with subcortical volumes or functional connectivity measures.
Conclusion: Together, these findings suggest that early environmental contexts are differentially associated with neural and epigenetic phenotypes. Ongoing work will expand the sample to further clarify these relationships.

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Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.03/F1

Topic: A.07. Development of Neural Systems

Title: The essential role of ketones in the developing brain

Authors: *S. CHOLETTE-TÉTRAULT[1], A. LEBLANC PIETTE[2], K. ZEMMOUR[3], K. J. FERNANDES[4], S. CUNNANE[1];
[2]Faculté de médecine et des sciences de la santé, [3]Dept. de Psychiatrie, [1]Univ. de Sherbrooke, Sherbrooke, QC, Canada; [4]Med., Univ. of Sherbrooke, Sherbrooke, QC, Canada

Abstract: The human brain is energetically expensive and proportionally even more so during early development. Most models of brain energy metabolism remain largely glucocentric, often presenting ketone bodies (i.e. acetoacetate and β-hydroxybutyrate) as secondary fuels used only during fasting, starvation, or metabolic stress. This adult-centered perspective may underestimate their physiological importance in the developing brain. We propose to re-examine the role of ketone bodies in early brain development, with particular attention to their dual contribution to energy metabolism and lipid biosynthesis. We performed a narrative synthesis of historical and

contemporary scientific literature on ketone uptake, transport, oxidation, and anabolic metabolism in the developing brain, emphasizing human and animal studies that have received limited attention in recent models of cerebral metabolism. The available evidence suggests that ketone bodies are not merely alternative fuels, but major metabolic substrates during early life. In the infant brain, ketones contribute meaningfully to ATP production and provide carbon for the endogenous synthesis of cholesterol and fatty acids required for membrane formation, myelination, and overall brain growth. These findings support a broader view of ketone metabolism as a normal feature of neurodevelopment rather than a marginal adaptation to energetic stress.Impaired ketone availability, transport, or utilization may therefore represent an underrecognized contributor to altered neurodevelopmental trajectories and vulnerability to neurological and psychiatric disorders. Reinserting ketone biology into models of human brain development may help clarify the evolutionary, developmental, and therapeutic relevance of ketone metabolism across neurology and psychiatry.

Disclosures: S. Cholette-Tétrault: None. **A. LeBlanc Piette:** None. **K. zemmour:** None. **K.J. Fernandes:** None. **S. Cunnane:** 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.; Nestlé Health Science, Alzheimer Association (USA), Baszucki Brain Research Fund, McConnell Foundation, Hecht Foundation.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.04/F2

Topic: A.01. Neurogenesis and Gliogenesis

Title: Characterizing Infant Feeding Contexts to Predict Early Structural Neurodevelopment

Authors: *B. LOCKHART, B. HOWELL;
Virginia Tech., Roanoke, VA

Abstract: Human milk (HM) represents one of the earliest and most dynamic environmental exposures influencing infant brain development. Beyond nutrition, HM is a complex biofluid shaped by maternal physiology, infant needs, and feeding behaviors. However, there is limited consensus regarding which dimensions of HM exposure, including feeding frequency, feeding duration, feeding mode, or cumulative measures of milk intake, most effectively capture biologically relevant variation associated with infant brain development. Identifying optimal measures of milk exposure is critical for advancing developmental neuroscience and improving the interpretation of infant feeding research.This work-in-progress analysis utilizes longitudinal data from 30 human-milk-fed mother-infant dyads followed from 3 to 12 months postpartum. Repeated assessments of feeding practices were collected alongside infant magnetic resonance imaging (MRI) acquired at 3, 6, and 12 months of age. Feeding measures included frequency of

feeds, duration of feeding episodes, and mode of feeding (direct breastfeeding, expressed HM, or mixed feeding practices). These data were used to generate multiple operational definitions of HM exposure, including average feeds per day, cumulative daily feeding duration, integrated frequency-duration metrics, stability of feeding patterns across infancy, and estimates of the proportion of the infant diet composed of HM.Infant brain growth was assessed using T1-weighted and T2-weighted MRI measures. Mixed-effects growth models and comparative predictive analyses will be employed to determine which measures of HM exposure best account for variability in infant brain development trajectories across the first year of life.We hypothesize that feeding frequency will emerge as a stronger predictor of volumetric brain growth than feeding duration alone, and that composite measures integrating multiple dimensions of feeding context will demonstrate superior predictive utility relative to single exposure metrics. Findings from this study will inform the selection of developmentally relevant HM exposure measures in future investigations of early nutritional influences on infant neurodevelopment.

Disclosures: B. Lockhart: None. **B. Howell:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.05/F3

Topic: A.06. Developmental Disorders

Support: Philantropic donation / Grant GR1001250 - McLean Hospital

Title: Acute Ethanol Exposure Induces Stage-Specific Bioenergetic, Mitochondrial and Neurodevelopmental Transcriptional Remodeling in Human Forebrain Progenitors

Authors: O. FOLORUNSO[1], A. LUSSIER[2], A. MACDONALD[3], M. MALIK[5], K. LAW[2], M. MILLET[4], J. SUH[5], K. J. RESSLER[6], C. PALMER[2], *J. GILBERT JARAMILLO[7];
[1]Dept. of Basic Neurosci., [2]McLean Hospital/Harvard Med. Sch., Belmont, MA; [3]McLean Hospital/Harvard Med. Sch., Anderson, SC; [4]McLean Hospital/Harvard Med. Sch., Acton, MA; [5]McLean Hosp., Belmont, MA; [6]Harvard Med. Sch., McLean Hosp. / Harvard Med. Sch., Belmont, MA; [7]Div. of Depression and Anxiety Disorders, McLean Hosp. - Harvard Med. Sch., Belmont, MA

Abstract: Prenatal alcohol exposure (PAE) is associated with long-term neurodevelopmental risk, yet how neuronal progenitor metabolism responds to alcohol across developmental stages remains unclear. Here, we integrated brain-isoform-focused analysis of public datasets with targeted transcriptional, translational, and functional mitochondrial assessments in human iPSC-derived cortical progenitor models representing distinct bioenergetic states. Re-analysis of prior PAE studies revealed broad metabolic gene downregulation in embryonic systems, whereas neurodevelopmental models showed limited and non-coherent transcriptional signatures. In vitro, we used the CRISPR corrected iPSC line (KOLF2.1J) to reduce confoundings driven by the

presence of neurodegenerative-associated mutations; some of which are in close relationship with mitochondrial dysfunctional phenotypes. We showed acute ethanol exposure (AEE) induced stage-dependent transcriptional remodeling in iPSC-derived neuronal progenitor cells. Early neuronal progenitors exhibited selective upregulation of mitochondrial-associated transcripts alongside increased neuronal lineage markers. In contrast, late neuronal progenitors showed broader increases in glycolytic, lipid, and mitochondrial gene expression. Despite these transcriptional changes, mitochondrial ATP production and mitochondrial protein abundance remained unchanged in both models with altered fusion-fission dynamics being restricted to late progenitors. These findings indicate that ethanol exposure is associated with developmental stage-dependent neuronal remodeling of bioenergetic genes. Lastly, measurements of mitochondrial-neural frameworks ~two days after AEE, showed no major alterations in either model. Overall, our results reveal a dissociation between transcriptional, translational, and functional bioenergetic outputs in models of early human neurodevelopment and highlight that transcriptional alterations of mitochondria and cellular bioenergetics under AEE should be interpreted in the context of developmental stage rather than in isolation as evidence of energetic dysfunction.

Disclosures: O. Folorunso: None. **A. Lussier:** None. **A. MacDonald:** None. **K. Law:** None. **M. Millet:** None. **J. Suh:** None. **K.J. Ressler:** None. **C. Palmer:** None. **J. Gilbert Jaramillo:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.06/F4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R35GM158124

Title: Developmental Windows of Sevoflurane Neurotoxicity in Human Brain Organoids

Authors: *E. DIAZ, I. MORALES PANTOJA, C. D. MINTZ;
Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Prolonged exposure to anesthetics and sedative drugs (ASDs) during early development has been shown in animal models to disrupt neural circuit maturation, induce neuronal injury, and contribute to long-term cognitive deficits, raising concerns about the neurodevelopmental safety of ASD. Our preliminary murine studies indicate that early postnatal exposure to isoflurane impairs cognition and disrupts newborn neuron development through the mTOR pathway. However, the mechanism by which anesthetic-induced neurotoxicity may alter human neurodevelopment remains unknown. To address this gap, we used human iPSC-derived brain organoids (HBOs) at distinct stages of differentiation to identify developmental windows of susceptibility to sevoflurane.

HBOs were exposed to 2.4% sevoflurane or to a carrier gas control consisting of 5% CO_2/95% air for 4 hours at weeks 4, 6, or 8 of development. A repeated-exposure group included HBOs from week 4 that were re-exposed at week 6. A standard culture condition, exposed to neither sevoflurane nor carrier gas, served as an additional control. Organoid function and phenotype were assessed using Ca^{2+} imaging (n=4, 17 HBOs per condition) and immunofluorescence (n=1, 7 HBOs per condition).
Sevoflurane exposure significantly altered Ca^{2+} flux dynamics. The mean Ca^{2+} transient peak amplitude increased by 50% two weeks after exposure at week 4. We next quantified neuronal and glial markers by immunofluorescence (mean intensity) at week 8 and observed a significant increase in immature oligodendrocytes (O4+) in sevoflurane-exposed groups, with no significant changes in astrocyte GFAP signal. The dendritic marker MAP2 decreased by ~25% two weeks after exposure and by ~48% following repeated exposure. In parallel, the neurofilament heavy chain (NF-H) increased by 16% two weeks after exposure. Postsynaptic Density Protein 95 (PSD95), a protein associated with synaptic plasticity, remained unchanged after a single exposure but decreased by 10% in the repeated-exposure group.
Because HBO-derived evidence in anesthesia neuroscience research remains sparse, this study provides important human-relevant insights into anesthetic-induced developmental neurotoxicity. Together, our findings support the possibility that discrete windows of vulnerability to anesthetic exposure exist during human brain development and may contribute to altered neural circuit formation.

Disclosures: E. Diaz: None. **I. Morales Pantoja:** None. **C.D. Mintz:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.07/F5

Topic: A.07. Development of Neural Systems

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Hong Kong Polytechnic University Internal Funding (1-CDJM)

Title: In Utero Functional Ultrasound Imaging Reveals Brain Activity in Embryonic Mice and Fetal Non-Human Primates

Authors: *J. ZHU[1], Z. QIU[2];
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Abstract: Investigating brain function during embryonic development has remained challenging due to limited access to the intact developing brain in vivo. Here, we establish functional ultrasound imaging (fUS) as a platform for monitoring brain activity during embryonic development in mice and fetal non-human primates.In mouse embryos, in utero fUS imaging was performed from embryonic day (E) 12.5 to E18.5. Following suppression of cardiac-related hemodynamic signals using frequency-domain deconvolution, spontaneous low-frequency fluctuations (<4 Hz) were consistently observed across forebrain, midbrain, and hindbrain regions. Cross-modal correspondence analyses using multi-electrode array recordings and wide-field calcium imaging at E18.5 revealed similar low-frequency temporal dynamics across modalities, supporting the ability of fUS to capture developmentally relevant functional activity patterns.To evaluate stimulus-associated responses, auditory stimulation (1, 10, and 16 kHz) was delivered to late-stage embryos. Sound presentation elicited localized cerebral blood volume responses in sensory-related brain regions, accompanied by corresponding calcium signal increases. Postnatal behavioral testing further demonstrated stimulus-associated motor responses following auditory stimulation. In addition, deep brain stimulation induced reproducible hemodynamic responses in targeted embryonic brain regions, demonstrating sensitivity to externally evoked neural activation.To assess translational feasibility, we extended fUS imaging to fetal cynomolgus macaques. In gestational day 85 fetuses, sound stimulation evoked localized hemodynamic responses in regions corresponding to immature sensory-related networks, providing a proof-of-principle demonstration of prenatal functional imaging in a non-human primate model.Together, these findings establish fUS as a non-invasive approach for investigating spontaneous and stimulus-associated brain activity during embryonic development across species. This framework provides new opportunities for studying functional brain maturation and may facilitate future investigations of neurodevelopmental disorders during early developmental stages.

Disclosures: J. Zhu: None. **Z. Qiu:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.08/F6

Topic: A.07. Development of Neural Systems

Support: R21HD111858

Title: Whole-brain mapping reveals transient reduction of oxytocin neurons in the accessory nucleus of mouse in offsprings after oxytocin-induced birth in mice

Authors: *L. SUN;
Penn State Univ., Hershey, PA

Abstract: Whole-brain mapping reveals transient reduction of oxytocin neurons in the accessory nucleus of mouse in offsprings after oxytocin-induced birth in mice

***Lihao Sun**[1], Tusar Giri[2], Gokhan Serce[2], Arvind Palanisamy[2], Yongsoo. Kim[11]Department of Neuroscience and Experimental Therapeutics, College of Medicine, The Pennsylvania State University, Hershey, PA, USA[2]Division of Obstetric Anesthesiology, Washington University in Saint Louis, St. Louis, Missouri, USA

Maternal oxytocin (OXT) administration is widely used for labor induction, yet its impact on OXT neurocircuitry in the offspring remains poorly understand. OXT neurons within hypothalamic circuits regulate social behaviors, stress responses, and developmental processes, raising concerns that perinatal OXT exposure could have lasting neurodevelopmental effects. Previous studies suggest that perinatal OXT exposure can alter early social communication behaviors in offspring (Giri et al., 2024), highlighting the need to define underlying circuit-level changes. Here, we aim to elucidate the effects of maternal OXT administration on hypothalamic OXT neurocircuitry in mouse offspring. Pregnant dams received continuous intravenous OXT administration on gestational day 19 via iPrecio pump to induce and augment labor. Offspring brains were collected at postnatal day 14 (P14), representing an early developmental stage, and P56, representing adulthood. Whole-brain OXT neuron mapping was performed using tissue clearing, 3D staining with oxytocin antibody, light-sheet microscopy imaging, and quantitative whole brain analysis. Our results revealed reduced OXT neurons within the accessory hypothalamic nucleus in OXT-exposed offspring at P14 compared with controls. In contrast, no significant differences were detected in major hypothalamic OXT-producing regions, including the paraventricular hypothalamic nucleus (PVH) and supraoptic nucleus (SON), indicating region-specific developmental sensitivity to maternal OXT exposure. By P56, no significant differences were detected across OXT-associated regions, suggesting normalization of OXT neuron numbers during maturation. These findings demonstrate that maternal OXT exposure transiently alters developmental organization of hypothalamic OXT circuitry during early postnatal development despite apparent recovery of overall OXT neuron numbers by adulthood. These results highlight developmental vulnerability of offspring OXT neural circuits to perinatal maternal interventions and underscore the importance of evaluating potential long-term neurobiological consequences associated with maternal OXT exposure.

Disclosures: L. Sun: None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.09/F7

Topic: A.06. Developmental Disorders

Support: NINDS R01NS121660
NIAAA P50AA022534 NMARC Pilot 6B
UNM Center for Brain Recovery and Repair (CBRR) NIGMS P20GM109089 grant

Title: Third Trimester-Equivalent Alcohol Exposure Induces Sex-Dependent Alterations in Locomotor Activity, Anxiety-Risky Behaviors, and Enhances Mechanical Allodynia in Adulthood

Authors: *E. VILLICANA[1], M. S. SUN[5], H. CHEN[2], L. PAEZ-BELTRAN[7], R. A. MORTON[3], E. D. MILLIGAN[4], C. F. VALENZUELA[8], T. VUE[6];
[2]Neurosci., [3]Neurosciences, [4]Dept Neurosci, [1]Univ. of New Mexico, Albuquerque, NM; [5]Neurosciences, [6]Dept. of Neurosciences, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [7]Univ. of New Mexico Dept. of Neurosciences, Albuquerque, NM; [8]Dept Neurosci, Univ. New Mexico HSC, Albuquerque, NM

Abstract: Prenatal alcohol exposure (PAE) causes fetal alcohol spectrum disorders (FASDs), which are neurodevelopmental conditions characterized by behavioral dysregulation, learning deficits, and cognitive inflexibilities. Alcohol exposure is harmful at all stages of human gestation, including the third trimester. This developmental window—characterized by rapid brain growth,
myelination, and neural circuit formation—may be particularly vulnerable, yet the long-lasting behavioral and sensory consequences of exposure during this period remain poorly understood. In this study, neonatal mouse pups were exposed to ethanol (EtOH) or air vapor from postnatal day (P) 4 to P8, which is equivalent to a third-trimester alcohol exposure (TTAE) in humans. Blood ethanol concentrations measured at P8 reached approximately 250 mg/dL, consistent with binge-level exposure. Air- and EtOH-exposed mice were then assessed as adults at 5-6 months of age for locomotor activity, anxiety-related risky behaviors, recognition memory, and increased susceptibility to peripheral neuropathy, as indicated by sensitization to light touch following minor chronic constriction injury (mCCI) of the sciatic nerve. We found that TTAE was sufficient to produce long-lasting behavioral outcomes in a sex-dependent manner. Notably, EtOH-exposed males exhibited increased spontaneous locomotor activity and risky behavior, whereas EtOH-exposed females showed minimal or decreased changes compared to their respective controls. However, both EtOH-exposed male and female mice exhibited marked increases in light-touch sensitization, referred to as mechanical allodynia, following mCCI, a response absent in air-exposed controls. Together, these findings reveal that TTAE is highly detrimental to behavioral regulation and creates a vulnerability to developing neuropathic pain in adulthood.

Disclosures: E. Villicana: None. **M.S. Sun:** None. **H. Chen:** None. **L. Paez-Beltran:** None. **R.A. Morton:** None. **E.D. Milligan:** None. **C.F. Valenzuela:** None. **T. Vue:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.10/F8

Topic: A.02. Stem Cells and Reprogramming

Support: NIH NINDS R01 NS125778

Title: Peli1 promotes ZIKV-induced neurodevelopmental injury and neural stem cell depletion

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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 relatively low infection rate does not fully explain the extent of damage observed in the developing 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 significantly reduced Sox2+ NSC numbers and produced a near-significant reduction in Ki67+ proliferating cells in WT embryos, consistent with impaired neurogenesis. In contrast, PKO embryos exhibited increased Sox2+ cell numbers and reduced morphological abnormalities following ZIKV infection, suggesting attenuation of ZIKV-induced developmental defects. In parallel, immunohistochemistry of yolk sac tissue revealed that ZIKV reduced the number of F4/80+ yolk sac macrophages, an effect attenuated in PKO embryos, suggesting that Peli1 contributes to depletion or dysregulation of early microglial progenitors. Analysis of embryonic brain cytokines revealed only modest induction of inflammatory mediators following ZIKV infection, while Peli1 deficiency significantly reduced cytokine expression, indicating that Peli1 contributes to the inflammatory response but may also mediate neurodevelopmental injury through additional mechanisms. To investigate said mechanisms, primary microglia and NSPC co-culture systems were established to examine microglia-mediated viral transmission and regulation of NSPC growth. Ongoing studies are evaluating whether ZIKV-infected microglia transmit virus to NSPCs and how ZIKV infection and Peli1 deficiency alter microglia-dependent effects on NSPC proliferation and survival. Together, these findings support a model in which Peli1-dependent microglial responses contribute to ZIKV-induced neurodevelopmental damage and neural stem cell loss. This work provides insight into how non-neuronal cells contribute to congenital viral syndromes and identifies Peli1-dependent microglial pathways as potential therapeutic targets for protecting the brain.

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

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.11/G1

Topic: A.07. Development of Neural Systems

Support: Israel Science Foundation 746/24

Title: Temporal Dynamics of Memory Amplification and Its Suppression Through Pharmacological Intervention

Authors: *A. AHIRE[1], D. DAPHNE[2], I. REUVENI[1], E. BARKAI[1];
[1]Sagol Dept. for Neurobio., Univ. of Haifa, Haifa, Israel; [2]Natl. Ctr. for Drug addiction and Drug Abuse (NIDA), NIH, Baltimore, MD

Abstract: Temporal Dynamics of Memory Amplification and Its Suppression Through Pharmacological InterventionBackground: We recently reported an experimental and theoretical evidence for a long-term mechanism that amplifies the response of a subset of neurons that were recruited during the learning of a complex task. We have termed this mechanism as "**memory amplification mechanism**". This mechanism is mediated by doubling of the strength of all inhibitory and all excitatory synapses in the cell. The key function of the amplification mechanism is to promote an already formed memory to a dominant memory. CaMKII phosphorylation at ser831 doubles AMPA channel current by increasing conductance, similar to amplification mechanism induction. We aimed to inhibit this phosphorylation using a competitive blocker to potentially reverse increased conductance and modulate or suppress the amplification mechanism. **Aim:**Using TRAP2 genetically modified mice, we are investigating the long term retention of the traumatic memory through amplification mechanism and target pharmacologically to modulate or suppress its effect. **Methods:**1.The fear condition training had been conducted for 2 consecutive days, where on both days the animal was exposed to 6 pairs of conditioned trial. Retrieval was analyzed over 8 weeks at specific intervals to assess long-term retention of the amplification mechanism.
2.We recorded miniature synaptic events via whole-cell patch clamp recordings from neurons in the lateral amygdala of a transgenic mouse model expressing TRAP2/fos fluorescence cells after fear-memory retrieval.
3.Competitive blocker of ser831 was administered before the 5th day of retrieval to investigate its effect on memory amplification.
Results: Freezing due to traumatic memory persisted for 8 weeks post extensive training. Additionally, synaptic current amplitudes increased selectively in neurons tagged with TRAP2/fos after fear-memory retrieval. Preliminary results indicate that the competitive blocker of ser831 reduces freezing time even after extensive training.**Conclusion:**Taken together with our previous findings, the dominant aversive memory is maintained by a sub-group of neurons on which all synaptic inputs, inhibitory and excitatory are doubled. The board strengthening is controlled by a whole-cell rather by a synaptic specific process and is mediated by post synaptic CaMKII mediated enhanced channel conductance. A competitive blocker targeting Ser831 emerges as a potential candidate to suppress this amplification mechanism.

Disclosures: A. Ahire: None. **D. Daphne:** None. **I. Reuveni:** None. **E. Barkai:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.12/G2

Topic: A.07. Development of Neural Systems

Support: TSRI RCDF -000017553
R01 DK126085

Title: Adaptation of Developing Vagal Circuitry to Early Life Adversity

Authors: *S. PANVINI[1,2], S. KAMARA[2], M. HONG[2], P. LEVITT[2];
[1]Children's Hosp. of Los Angeles, Glendale, CA; [2]Pediatrics, The Saban Res. Institute, Children's Hosp. of Los Angeles, Los Angeles, CA

Abstract: Early life adversity (ELA) is a leading preventable cause of morbidity and mortality, increasing the risk for mental and physical health conditions later in life. The impact of ELA on the etiology of brain-body disorders remains unclear. We hypothesized that ELA alters the development of vagal circuitry, a major anatomical conduit for brain-body communication. Using the limited bedding and nesting (LBN) ELA mouse model of unpredictable maternal care (P2-P9), we assessed effects on 1) the development of vagally mediated parasympathetic stress response and 2) transcriptomic profiles of the dorsal vagal complex (DVC) within the brainstem. Three different metrics of heart rate variability (HRV) were used to measure the vagally mediated response to a mild novelty-induced environmental stressor. The ECGenie system was used to measure HRV metrics non-invasively in freely behaving mice longitudinally at P9, P21, P35, P55, and P120. Single-nucleus RNA sequencing (snRNAseq) of the DVC was performed at P9 and P120, followed by Hi-plex RNAScope to map spatial gene expression. ELA altered developmental trajectories of all HRV metrics with female ELA mice displaying flattened HRV trajectories beginning at P9 followed by significant adult declines compared to controls. Male ELA mice also exhibited initial flattening of HRV responses, but recovered to control levels by adulthood. Transcriptomic changes occurred across cell types, with marked sex differences. Enrichment analysis revealed that in P9 and P120 females, neurons displayed signatures of mitochondrial dysfunction, while males showed adaptive mitochondrial responses and profiles of buffering oxidative stress. Strikingly, spatial mapping of these transcripts revealed topographical, sex-dependent effects. Adaptive male responses were localized to neurons in the intermediate dorsal motor nucleus of the vagus, which projects to the heart to contribute to ventricular contractility, and thus HRV. Adaptive male responses also mapped to the rostral/transition zone of the nucleus of the solitary tract, which contains neurons responsible for integrating sensory signals from multiple organ systems and directly communicating to the dorsal motor nucleus, as part of the vago-vagal reflex arc in response to stress. Overall, ELA induces enduring, sex- and cell-type-specific alterations in vagal circuit development centered on mitochondrial pathways. Females exhibit susceptibility within these circuits, whereas males show adaptive cellular responses, potentially promoting autonomic stress resilience.

Disclosures: S. Panvini: None. **S. Kamara:** None. **M. hong:** None. **P. Levitt:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.13/G3

Topic: A.07. Development of Neural Systems

Support: NINDS 7R01NS126981

Title: Use of An Ex-Vivo organ perfusion system to study placental prostaglandin release and effects on the fetal brain

Authors: *J. ALVAREZ[1], H. HORACKOVA[2], Q. ZHAO[3], A. BONNIN[4];
[1]USC, Los Angeles, CA; [2]Children Hosp. Los Angeles, Saban Res. Institute, Univ. of Southern California, Los Angeles, CA; [3]Univ. of California, LA, Los Angeles, CA; [4]Cell and Neurobio., USC - ZNI, Los Angeles, CA

Abstract: Maternal immune activation (MIA), an inflammatory response to an infection during pregnancy, is associated with increased risk for neurodevelopmental disorders in the offspring. Our previous study identified prostaglandin-dependent MIA-induced disruptions in fetal blood brain barrier (BBB) vascular structure, leading to increased permeability. Mechanistically, MIA led to an increase in cyclooxygenase-2 (COX-2) enzymatic activity in the placenta and an increase in prostaglandin E2 (PGE2) in the fetal brain. PGE2 is synthesized via arachidonic acid, a phospholipid precursor released during inflammation, metabolism by COX-2 to PGH2, subsequently metabolized by prostaglandin E-synthase (mPGES1). We observed both COX2 and mPGES1 expression in the placenta. Using an ex-vivo mouse placenta perfusion model, we are testing if maternally derived arachidonic acid is metabolized to PGH2 and PGE2, and if these molecules are subsequently released into the fetal bloodstream and reach the fetal brain. In the context of MIA, such placentally derived PGE2 could trigger downstream fetal BBB disruptions. Mouse placentas at gestational day 14 were perfused through the uterine artery with arachidonic acid (2.5 mg/mL) to activate the COX-2 pathway. The output to the fetus was measured through the umbilical vein at various time points. Prostaglandin E2 (PGE2) and H2 (PGH2) release was measured using a high-sensitivity PGE2 ELISA.
Ex-vivo perfusions of arachidonic acid showed a dramatic increase in PGE2 release during the 20-40min (21.7 (±) 6.5ng/mL) and 40-60min (19.9(±)7 ng/mL) collections in comparison to the vehicle group (20-40min:1.37(±) 0.38ng/mL, 40-60min:1.33(±)0.48ng/mL, two-way ANOVA;(*$p<0.05$) n = 4). No significant release of PGH2 was measured through the umbilical vein (two-way ANOVA;(*$p>0.05$) n = 4). However, post-perfused tissue shows a trend of PGH2 accumulation in the decidual ($p=0.13$) and labyrinth ($p=0.35$) layers of the placenta in the arachidonic acid group (n=4). These results support evidence of increased PGH2 synthesis occurring in the placenta.
Our results demonstrate that the placenta metabolizes arachidonic acid to PGH2 and PGE2.

While PGH2 may not be released into the fetal bloodstream due to the rapid intermediary metabolization, placenta-derived PGE2 is released into the fetal bloodstream. This suggests that increased placenta-derived PGE2 release during MIA can alter downstream fetal BBB formation.

Disclosures: J. Alvarez: None. **H. Horackova:** None. **Q. Zhao:** None. **A. Bonnin:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.14/G4

Topic: A.07. Development of Neural Systems

Title: Maternal Perinatal Low-Protein High-Carbohydrate Diet Disrupts SCN Structure and Circadian Entrainment in Male Offspring

Authors: *D. J. BUSTAMANTE VALDEZ, M. FUENTES-CANO, K. OCAMPO ORTIZ, P. DURAN;
UNAM, Mexico, Mexico

Abstract: The suprachiasmatic nucleus of the hypothalamus (SCN) is the master oscillator in mammals, generating rhythms of approximately 24 hours. It can be entrained by various environmental cues, or Zeitgebers, such as food availability and light. Locomotor activity is an endogenous behavior that adjusts to these synchronization signals. Maternal nutrition is widely recognized as a key factor for optimal offspring development, particularly during critical developmental windows, as it induces short-, medium-, and long-term anatomical and physiological adaptations. Perinatal malnutrition alters the circadian rhythm of several physiological, metabolic, and behavioral processes; however, the underlying physiological mechanisms remain poorly understood. This study aimed to evaluate the effect of a perinatal maternal low-protein, high-carbohydrate diet on the structural and functional integrity of the SCN, as well as on the synchronization between central and peripheral circadian clocks as a mechanism of early metabolic programming. Female Sprague-Dawley rats were randomly assigned to two nutritional protocols: control (CO) and hypercaloric-low protein (DCa), and maintained with food and water *ad libitum* for three weeks prior to mating, as well as during gestation and lactation. All evaluations were performed on young male offspring. Postnatal body weight and size were recorded from birth to adulthood. Locomotor activity was recorded under LL and DD conditions. Additionally, neuronal density and the circadian expression of clock genes in the SCN were evaluated. Our results show that the DCa group exhibited a decrease in body weight and size, reduced SCN neuronal density, and alterations in rhythm amplitude and mesor. Compared to the CO group, the DCa group displayed a significantly increased period in DD and a greater number of transient days during re-entrainment to LD. These findings demonstrate a structural and functional mismatch of the central oscillator as a potential fundamental mechanism in developmental programming, providing new insights into the early origins of physiological and behavioral dysfunction.

Disclosures: D.J. Bustamante Valdez: None. **M. Fuentes-Cano:** None. **K. Ocampo Ortiz:** None. **P. Duran:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.15/Web Only

Topic: A.07. Development of Neural Systems

Support: CONAHCyT CF-2023-G-148
INPer 2024-1-34

Title: EFFECT OF MATERNAL HYPERGLYCEMIA ON FOXP2EXPRESSION AND THE DEVELOPMENT OF MOTOR CIRCUITSINVOLVED IN ULTRASONIC VOCALIZATIONS IN THE RAT

Authors: *R. VALLE-BAUTISTA[1], V. RODRÍGUEZ-SUAREZ[2], M. JIMÉNEZ-BELTRÁN[3], L. GÓMEZ-GARCÍA[2], N. E. DIAZ[4], A. MOLINA[5];
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Abstract: Gestational Diabetes Mellitus (GDM) affected 20.4 million births worldwide in 2019,representing 15.8% of all live births. GDM has been associated with delayed motordevelopment and language deficits in the offspring of diabetic mothers. In a previous studyfrom our group, the offspring of diabetic rats (Db) showed an increased number ofpyramidal neurons in layers V and VI of the primary motor cortex (M1), evidenced byincreased expression of the transcription factors FoxP2 and Tbr1 at postnatal day 21 (P21).Additionally, these neurons exhibited reduced dendritic arborization and lower excitabilitycompared with the control group (Ctrl), suggesting that cortico-striatal and cortico-ponto-cerebellar circuits involved in motor and communication processes may be altered in theoffspring of diabetic rats. FoxP2 is involved in the development and maturation of braincircuits required for proper language development in humans and for the emission ofultrasonic vocalizations (USV) in rodents. In rats, the primary structures involved in thesecircuits are the M1 cortex, the striatum, and the cerebellum, all of which express FoxP2abundantly. In humans, the R553H mutation in the FoxP2 gene produces a verbal dyspraxiaphenotype characterized by severe impairments in the selection and execution of orofacialmovements required for speech articulation, whereas rodents display deficits in motor skilllearning and in USV emission. In the context of motor function development involved inUSV learning, the role of FoxP2 in the cerebellum remains unclear. In this regard, FoxP2-R552H/+ mice exhibit reduced neonatal USV emission accompanied by alterations inparallel fiber plasticity, reduced cerebellar foliation, and decreased dendritic arborization ofPurkinje cells.Therefore, the aim of this study is to determine the effect of maternalhyperglycemia on

postnatal FoxP2 expression in the M1 cortex, striatum, and cerebellum,as well as on USV emission in rats at P0 and P21. Preliminary results obtained from sagittalbrain sections of P21 rats show that female offspring from the Db group exhibit higherFoxP2 expression in the M1 cortex, striatum, and cerebellum compared with the Ctrl group,whereas male offspring show increased FoxP2 immunodetection in the M1 cortex andcerebellum. These findings suggest that the increase in FoxP2 expression induced by GDMmay alter the development of motor learning circuits in the offspring, potentially leading toabnormalities in USV emission patterns.

Disclosures: R. Valle-Bautista: None. **V. Rodríguez-Suarez:** None. **M. Jiménez-Beltrán:** None. **L. Gómez-García:** None. **N.E. Diaz:** None. **A. Molina:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.16/H1

Topic: A.07. Development of Neural Systems

Support: Bowling Green State University Elevate Grant

Title: Neurodevelopmental Effects of Perinatal Resveratrol Exposure in Male and Female Rats

Authors: *L. KINNEY[1], H. RUBY[2], S. BOSS[2], J. WILLING[3];
[1]Bowling Green State Univ., Perrysburg, OH; [3]Psychology, [2]Bowling Green State Univ., Bowling Green, OH

Abstract: Resveratrol is a dietary supplement that is marketed to aged individuals, as it has been shown to slow neurocognitive decline in animal models. It has a variety of mechanistic actions that include anti-inflammatory, anti-oxidative, and anti-apoptotic effects. Its ability to reduce inflammation and oxidative stress has made it a popular supplement for other health issues, including pregnancy-related conditions. The perinatal period of brain development is highly susceptible to environmental factors, and previous work shows that Resveratrol can cross the placenta and accumulate in milk during lactation. However, almost no studies have investigated Resveratrol's influence on the perinatal brain following maternal supplementation. We have previously shown that one relevant dose of resveratrol during development increases total brain size relative to controls. The present study expanded on these results by exposing pregnant Long Evans rats to Resveratrol at two different relevant doses throughout their gestational and lactational periods until postnatal day (P)10. At P5, P7, and P9, pups underwent behavioral testing to assess sensorimotor development. Brain tissue was collected at P2 and P10 for gene expression and neuroanatomical analyses. Results show that perinatal resveratrol exposure alters both neuroanatomical and behavioral development. The findings of this study will contribute to the knowledge of Resveratrol's safety and effectiveness during pregnancy and may shed light on its potential use as a supplement to treatments for neurodevelopmental disorders.

Disclosures: L. Kinney: None. **H. Ruby:** None. **S. Boss:** None. **J. Willing:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.17/H2

Topic: A.07. Development of Neural Systems

Support: ANRF, New Delhi (grant no. SUR/2022/001671)

Title: Impact of prenatal valproate exposure on Klotho expression and NLRP3-driven neuroinflammation in rodent model of Autism spectrum disorder

Authors: *S. RAHI, S. P. SAH;
Pharmacol. Div., Univ. Inst. of Pharmaceut. Sciences, Panjab Univ., Chandigarh, India

Abstract: World is currently experiencing a rapid epidemic of neurological illnesses. Autism spectrum disorder (ASD), is a lifelong neurodevelopmental disorder that typically demonstrate early delays in sensorimotor development, communication, and social relation which predict subsequent cognitive and behavioural outcomes. Globally, ASD affects 1 in 36 children, with males exhibiting a 3.8-fold higher prevalence than females. Despite extensive research, the etiology of ASD is still unclear with multiple contributing factors including activation of NLRP3 inflammasomes, which promotes interleukin (IL)-1β and IL-18 mediated inflammatory signalling. Klotho (KL), a pleiotropic anti-ageing and neuroprotective protein expressed in brain and circulates in both serum and cerebrospinal fluid, promotes neuronal proliferation, differentiation, survival and synaptic formation. It negatively regulates NF-κB/NLRP3 signalling and oxidative stress. However, the correlation between KL and NLRP3 activation in ASD is still unexplored. Thus, our study for the first time hypothesizes that KLOTHO downregulation in ASD may upregulate NLRP3 inflammasome signalling, resulting in neuroinflammation and early developmental deficits. Using the prenatal valproic acid (VPA, 600 mg/kg) rat model of ASD, we evaluated physical maturation, sensorimotor development and behavioural changes in offsprings and quantified series of biochemical and molecular estimation in serum, hippocampus, and cortex. Histopathological evaluation was also conducted to further confirm the visual changes in the stained brain sections. Our preliminary results demonstrated that VPA-exposed offsprings exhibit delayed physical growth and impaired sensorimotor development accompanied by behavioural deficits including reduced social interaction and increased repetitive behaviour. Furthermore, molecular analyses demonstrated significant downregulation of KL expression and corresponding increased expression of NLRP3 and associated cytokines (Caspase 1, IL-1β). Histopathological analysis revealed neuronal degeneration, cellular shrinkage and increased neuroinflammatory changes like pyknosis and vacuolation in the VPA treated animals in comparison to controls. These finding identify the KLOTHO-NLRP3 axis as a critical mechanistic link between neuroinflammation and ASD. Further in-depth understanding of this signalling cascade is required to provide insights into the molecular basis of ASD and their potential as therapeutic targets and diagnostic biomarker.

Disclosures: S. Rahi: None. **S.P. Sah:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.18/H3

Topic: A.07. Development of Neural Systems

Support: NIH Grant R01HD111737
COBRE P20GM103653

Title: Developmental Consequences of Cesarean Birth and Perinatal Hormone Signaling on Energy Balance and Striatal Dopaminergic Function in Adult Prairie Vole and Rat Offspring

Authors: *K. ROGERS[1], M. ROBBINS[1], S. M. FREEMAN[2], W. KENKEL[1];
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Abstract: Infants born by Cesarean section (CS) experience reduced perinatal oxytocin (OXT) levels after birth compared to vaginally delivered (VD) infants. Preclinical studies show altered dopamine (DA) -related neurobehavioral outcomes in CS offspring. DA system development is sensitive to perinatal OXT manipulations; however, whether neonatal hormone treatment can normalize the DA system in CS offspring remains unknown. Understanding the role of hormone signaling in development after CS birth may provide a mechanistic link to the increased prevalence of CS-associated neurodevelopmental and metabolic disorders. Because birth involves coordinated hormone signaling, offspring received a single injection of either OXT + vasopressin (AVP), to partially restore the hormonal milieu, or OXT alone, to isolate OXT-specific effects. As DA underlies reward, feeding, locomotion, and motivation, we examined body weight, food intake, and operant responding in adult prairie vole and rat offspring delivered vaginally or by CS following neonatal treatment with saline, OXT+AVP, or OXT. DA markers were characterized, including tyrosine hydroxylase (TH) -immunoreactivity (ir) and dopamine transporter (DAT) density, in the nucleus accumbens (NAc) and caudal caudate-putamen (cCP). CS rat and vole offspring showed greater body weight than VD offspring, a phenotype preliminarily ameliored by neonatal hormone treatment. CS-born voles also showed reduced locomotor activity relative to VD voles, while CS OXT+AVP-treated voles briefly superseded both VD and CS subjects. These findings suggest increased body weight in CS subjects, which was ameliorated by partial restoration of neonatal hormone conditions, may reflect altered energy balance resulting from reduced expenditure. In the cCP, CS voles had greater TH-ir than VD voles, which was ameliorated by neonatal OXT+AVP treatment. This increase may reflect compensatory, region-specific reorganization of dopaminergic function, potentially contributing to reduced locomotor activity and subsequently increased body weight in CS offspring. These findings have translational health relevance for widely used obstetric practice.

Disclosures: K. Rogers: None. **M. Robbins:** None. **S.M. Freeman:** None. **W. Kenkel:** None.

Poster

PSTR342: Pre- and Perinatal Impacts on Neurodevelopment

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.19/H4

Topic: A.07. Development of Neural Systems

Title: Centrosome mislocalization activates the YAP1 pathway to promote the neurodevelopmental process in Huntington's disease pig model

Authors: *C. HUANG[1,3], J. WU[4], X. LI[5], S. YAN[2];
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Abstract: Huntington's disease (HD) is a genetic neurodegenerative disease caused by mutations in the *Huntingtin* gene (*HTT*). The mHTT expressed at the beginning of HD embryonic development can affect the development of the nervous system and alter the progression of HD disease. We used single-cell sequencing to establish a single-cell atlas of the brain during the E40 stage of embryonic development in WT/HD-KI pigs, and found abnormal proliferation of excitatory neurons during their neural development. The abnormal localization of centrosomes in the Ventricular Zone (VZ) region activates YAP1, promoting the transformation of radial glial progenitor cells into intermediate progenitor cells, leading to accelerated neural development. When Yes-associated protein 1 (YAP1) is inhibited in neurons of HD-KI pigs and iPSCs of patients, abnormal axonal development is improved. This study elucidates how mHTT plays a role in the occurrence and development of HD by affecting neural development, providing potential targets for early prevention and treatment strategies of HD.

Disclosures: C. Huang: None. **J. Wu:** None. **X. Li:** None. **S. Yan:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.01/H5

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

Title: Modulation of EAAT1 and EAAT2 Transporter Expression by Histamine H3 Receptor Activation in Primary Cultured Rat Cortical Astrocytes

Authors: *E. HERNANDEZ FLORES;
FISIOLOGÍA, CENTRO DE ESTUDIOS SUPERIORES DE TEPEACA, Chalchicomula de Sesma, Mexico

Abstract: Motivation/ProblemStatement Glutamate is the main excitatory neurotransmitter in the central nervous system and is essential for synaptic plasticity, learning, and memory. However, sustained high extracellular levels induce excitotoxicity, contributing to neurodegenerative diseases such as Alzheimer's, Parkinson's, multiple sclerosis, and amyotrophic lateral sclerosis. Astrocytes regulate extracellular glutamate through EAAT1 and EAAT2 transporters, and their dysfunction promotes neuronal hyperexcitability and cellular damage. G protein-coupled receptors such as the histamine H3 receptor (H3R) modulate protein expression and may influence glutamate transporter regulation, representing a potential therapeutic target.**Methods/Approach**Primary astrocyte cultures were obtained from the cerebral cortex of Wistar rats (2-7 days postnatal) following NOM-062-ZOO-1999. Tissue was enzymatically (trypsin/EDTA) and mechanically dissociated and cultured in supplemented DMEM/F12 at 37°C and 5% CO_2 until 95% confluence. Cells were reseeded for analysis. Protein quantification was performed using the bicinchoninic acid method. EAAT1 and EAAT2 expression was analyzed by SDS-PAGE and Western blot with chemiluminescent detection and densitometric analysis using ImageJ. Immunofluorescence assays were conducted using antibodies against EAAT1 and GFAP, with DAPI staining and confocal microscopy.**Results**H3R activation modulated EAAT1 and EAAT2 expression in cortical astrocytes, evidenced by changes in protein band intensity in Western blot and variations in fluorescence signal patterns observed by confocal microscopy.**Conclusion/Implications**H3R activation modulates glutamate transporter expression in astrocytes, highlighting their role in controlling excitotoxicity. These findings support H3R as a potential therapeutic target in neurodegenerative diseases and suggest that modulation of EAAT1 and EAAT2 may contribute to neuroprotective strategies aimed at preserving synaptic function and reducing neuronal damage.

Disclosures: E. Hernandez flores: None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.02/H6

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

Support: NIH Grant R01MH129294
NIH Grant R01MH130367

Title: A population of septal glutamatergic PV-expressing cells excites the hypothalamic supramammillary nucleus

Authors: *H. LI[1], Q. SUN[2];
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Abstract: Parvalbumin (PV), a calcium-binding protein, has long been used as a canonical marker for fast-spiking GABAergic inhibitory neurons in the central nervous system. PV^+ neurons in the medial septum (MS) are well known to be pacemakers for the hippocampal theta oscillations through the septo-hippocampal GABAergic projection, playing critical roles in supporting hippocampal functions in learning and memory. Despite the recent identification of glutamatergic PV^+ neurons in a few cortical and subcortical regions, the potential existence of glutamatergic PV^+ neurons in MS is unknown. Here, we report a surprising discovery of a population of excitatory PV^+ neurons in MS of mouse brain. *In situ* hybridization revealed a notable fraction (26.8%) of *Pvalb* mRNA-expressing MS cells that express *Slc17a6* mRNA, a canonical glutamatergic neuron marker. Neural tracing and optogenetic-assisted *ex vivo* brain slice electrophysiology established that a population of MS PV^+ neurons projects and sends excitatory drive to the supramammillary nucleus, a hypothalamic subarea that is heavily interconnected with MS and the hippocampus. Strikingly, these supramammillary-projecting MS PV^+ neurons do not send collateral projections to the hippocampus, suggesting they represent a subtype of MS PV^+ neurons distinct from the well-known septo-hippocampal PV^+ GABAergic neurons. Unlike the typical fast-spiking, putative GABAergic MS PV^+ neurons, the supramammillary-projecting MS PV^+ neurons exhibited intrinsic firing patterns that are similar to those of the MS glutamatergic neurons. This discovery challenges a prevailing view that MS PV^+ neurons are uniformly GABAergic and inhibitory, further uncovering the functional heterogeneity of MS PV^+ neurons. It will also advance our understanding of the complex and heterogeneous roles of MS PV^+ neurons in the limbic system and hippocampal theta rhythms.

Disclosures: H. Li: None. **Q. Sun:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.03/H7

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

Support: NIH grant DK-109382

Title: VMN GHRH Neuron Transcriptomic and Counterregulatory Responses to Hypoglycemia and GAD2/GAD65 Silencing in Female Rats

Authors: *S. SAPKOTA[1], M. PASULA[2], K. P. BRISKI[3];
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Abstract: Hypoglycemia is a frequent complication of insulin therapy with a high chance of recurrent episodes. It can impair cognition, increase cardiovascular risk and may lead to coma if not corrected rapidly. Counterregulatory mechanisms driven by the brain, including cortisol, glucagon and growth hormone, are therefore pivotal to restoring the glucose. Within this system, mediobasal hypothalamus and VMN integrate metabolic, hormonal, and neurochemical cues to coordinate whole-body glucose homeostasis. Gamma-aminobutyric acid (GABA) reportedly acts by unidentified VMN mechanisms to suppress hypoglycemia-associated counterregulatory endocrine functions in female rats. We hypothesize that female-specific VMN GABAergic neurotransmission of dorsomedial VMN (VMNdm) growth hormone-releasing hormone (GHRH) neurons function via counterregulatory signaling to control this hormone outflow. We test this hypothesis using a GAD2/GAD65 siRNA knockdown model.Adult female rats(n=6/group) were bilaterally injected with scramble/siRNA after ovariectomy, followed 7 days later by vehicle or insulin and decapitation 1hr later with collection of blood. Fresh-frozen transverse VMN sections of 10 μm or 100 μm thickness were cut respectively, for mounting on membrane covered slides for immunohistochemistry followed by laser-catapult-microdissection/single-cell multiplex qPCR and micropunch samples for western blotting.GAD2 siRNA significantly reduces GAD mRNAs and protein, confirming silencing. qPCR results of Ghrh neurons showed pretreatment with siRNA intensified insulin induced hypoglycemia (IIH)-associated upregulation of Ghrh, Ghrh-R, n NOS and CYP19A1mRNAs transcripts. Estrogen receptors (ESR1, ESR2, GPER) were augmented in IIH-associated groups, pretreated with GAD2 siRNA indicating the enhanced estrogenic responsiveness when GABA tone is reduced. 5′-AMP-activated protein kinase alpha-1(PARKAA1) and alpha-2 (PRKAA2) gene expression were increased by IIH and magnified by siRNA pretreatment indicating disinhibition of counterregulatory-enhancing energy-sensor genes. IIH associated augmentation of glucagon and corticosterone were blunted by GAD2 knockdown, whereas GH was higher after siRNA treatment in both glycemic conditions.The study highlights the intricate interplay between GAD2 activity and neuroendocrine regulation. Further effort is needed to characterize the impact of GABA-dependent neurotransmission by this discrete VMN neuron on neural circuitries that govern glucose homeostasis.

Disclosures: S. Sapkota: None. **M. Pasula:** None. **K.P. Briski:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.04/H8

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

Support: Paul and Daisy Soros Fellowship for New Americans
SfN Neuroscience Scholars Fellowship
NIH Grant R01 NS129549
NIH Grant R42 NS125895

Title: Electrical stimulation of the infralimbic cortex differentially modulates dopamine dynamics in the rodent nucleus accumbens shell

Authors: *J. M. ROJAS CABRERA[1,2], C. D. BLAHA[1], Y. OH[1,4], H. S. MAYBERG[5], K. H. LEE[1,3,6], H. SHIN[1,3];
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Abstract: Dopamine (DA) signaling in the nucleus accumbens shell (NAcS) plays a critical role in mood regulation and reward processing via two distinct firing dynamics: phasic burst-firing of mesolimbic DA neurons which encode reward prediction errors, and tonic firing which establishes ambient extracellular DA levels that set the motivational threshold. Indeed, low DA tone in NAcS has been proposed as an underlying cause of anhedonia by reducing the motivational drive to engage in rewarding activities. Notably, while anhedonia is a common symptom of depression, individuals with treatment-refractory depression (TRD) show higher prevalence rates and greater severity. For these patients, deep brain stimulation (DBS) of the subcallosal cingulate cortex (SCC) has emerged as a promising treatment. Despite its clinical efficacy improving hedonic tone, the mechanisms mediating the therapeutic effects of SCC-DBS are not fully understood. It is hypothesized that DBS ameliorates anhedonia by normalizing DA-mediated reward-seeking behavior through modulation of the SCC's projections to mesoaccumbal neurons in the ventral tegmental area (VTA) and NAcS.
To test this hypothesis, phasic and tonic extracellular DA levels in the NAcS were monitored using fast-scan cyclic voltammetry (FSCV) and multiple-cyclic square-wave voltammetry (M-CSWV) during electrical stimulation of infralimbic cortex (ILC; SCC rodent homolog) in urethane-anesthetized rats. Brief trains of low-frequency (20Hz, 20s) stimulation evoked robust phasic DA efflux and was confirmed by DA transporter blockade with GBR 12909 (20mg/kg, i.p.). No significant differences in phasic DA response and female estrus cycle phase were noted. Interestingly, DBS-like stimulation (130Hz, 1hr) had no effect on tonic DA levels, suggesting the therapeutic effects of SCC-DBS on anhedonia may be mediated through other neurochemical substrates like accumbal serotonin or upstream circuitry. Future work will investigate the influence of DA modulation in the NAcS and prefrontal cortex with DBS and receptor-specific manipulations in disease-like models to assess their influence on the reward-seeking or pleasure-feeling subdomains of anhedonia, thereby elucidating SCC-DBS circuit mechanisms that may improve future treatment strategies.

Disclosures: J.M. Rojas Cabrera: None. **C.D. Blaha:** None. **Y. Oh:** A. Employment/Salary (full or part-time):; NaviNetics Inc.. **H.S. Mayberg:** None. **K.H. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NaviNetics, Inc.. **H. Shin:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.05/I1

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

Support: VA Merit BX001149
VA BX 001149 BRAVE supplement
VA BETS OP2026-08019
VA Research Career Scientist BX 004475

Title: Antidepressant properties of psychedelics; A common cellular pathway?

Authors: A. GUNAY[1], H. HALE[2], O. A. AJILORE[3], ***M. M. RASENICK**[4];
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Abstract: Psychedelics produce rapid and sustained reductions in depressive symptoms following a single administration, with therapeutic effects lasting weeks to months in clinical trials. Translocation of the Gsα protein from lipid raft microdomains to non-raft regions of the plasma membrane, where Gsα more efficiently couples to adenylyl cyclase and elevates intracellular cAMP, is a well-characterized molecular signature engaged by monoaminergic antidepressants and ketamine. Here, we tested whether the psychedelics psilocin or LSD engage this same pathway. C6 glioma and SK-N-SH neuroblastoma cells were treated with psilocin, LSD, or fluoxetine and Gsα-stimulated cAMP production was measured. Both psychedelics produced increases in cAMP comparable in magnitude to extended fluoxetine treatment despite requiring only brief exposure. Fluoxetine required three days incubation with these cells to show the same effect. The effects of psilocin and LSD on translocating Gsα from lipid rafts was also examined directly. A single 1-hour exposure to psilocin or LSD translocates Gsα from out of the rafts at 24 hours, with the effect persisting through 72 hours. While both psychedelics and fluoxetine had these effects, albeit with different time scales, none of these agents showed this "antidepressant biosignature" on the kidney epithelial HEK293 cell line, suggesting that neuronal or glial background is important for antidepressant action on the cellular level. These findings identify Gsα redistribution and enhanced cAMP signaling as a convergent cellular biosignature shared across pharmacologically diverse antidepressants, including psychedelics.

Disclosures: A. Gunay: None. **H. Hale:** None. **O.A. Ajilore:** None. **M.M. Rasenick:** A. Employment/Salary (full or part-time):; Pax Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pax Neuroscience. F. Consulting Fees (e.g., advisory boards); H.C. Wainwright.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.06/I2

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

Title: Comparative Effects of Simulated Lunar Red and Blue Light Cycles on Dopamine Secretion in SH-SY5Y Human Neuroblastoma Cell Cultures

Authors: *G. ROUHANI, J. CUTRO;
Sch. of Arts and Sci., MCPHS Univ., Boston, MA

Abstract: Environmental light serves as a powerful regulator of biological rhythms, neuronal activity, and neurochemical signaling. While the influence of daylight and artificial illumination on dopaminergic pathways has been extensively investigated, the neurochemical consequences of low-intensity nocturnal light environments remain poorly characterized. Naturally occurring moonlight represents a persistent environmental signal that has accompanied biological systems throughout evolutionary history, yet its effects on neurochemical regulation remain largely unexplored. Despite increasing interest in environmental photobiology, little is known about how lunar-spectrum wavelengths influence dopamine-related signaling at the cellular level.
This study investigates the effects of simulated lunar-spectrum blue light (450-470 nm) and red light (620-660 nm) on dopamine secretion in SH-SY5Y human neuroblastoma cell cultures. SH-SY5Y cells provide a well-established human neuronal model for examining dopaminergic function and neurochemical regulation. Cultures are maintained under standardized conditions and exposed to wavelength-specific blue-light, red-light, or dark-control environments that simulate lunar-like nocturnal light conditions. Following exposure, conditioned media are collected for quantification of extracellular dopamine concentrations using enzyme-linked immunosorbent assay (ELISA). Experimental conditions are standardized across treatment groups, and biological replicates are incorporated to support reproducibility and subsequent statistical comparison.
This study investigates whether distinct lunar-spectrum wavelengths differentially influence dopamine secretion under controlled in vitro conditions. Previous investigations have demonstrated wavelength-dependent effects of light on neuronal physiology, circadian regulation, and neurotransmitter-associated pathways, suggesting that spectral composition may represent an important but underexplored determinant of neurochemical activity. By examining dopamine secretion following exposure to simulated lunar red and blue light cycles, this project explores a novel intersection between environmental photobiology and dopaminergic regulation. Findings from this work may contribute to a broader understanding of how naturally occurring nocturnal light environments influence neurochemical signaling and biological timing mechanisms while establishing a foundation for future studies examining light-mediated modulation of neuronal function in increasingly complex biological systems.

Disclosures: G. Rouhani: None. **J. Cutro:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.07/I3

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

Support: NSF 2533202
NSF 2232510

Title: 5-HT1A autoreceptors modulate Drosophila behaviorat both larval and adult stages

Authors: B. POTTER[1], A. BELL[2], H. SCHNEIDER[2], T. FOX[2], A. URCUYO[1], M. BRANCH[1], I. LAMPERTI[1], E. WALKER[2], A. FERNUNG[2], *D. H. ROOSSIEN[1];
[1]Mount Holyoke Col., South Hadley, MA; [2]Ball State Univ., Muncie, IN

Abstract: Mood, sleep, appetite, and social interactions are a constellation of behaviors modulated by the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT). To accomplish this, 5-HT binds to serotonin receptors (5-HTRs), a family of GPCRs and ligand-gated ion channels that are expressed throughout the brain. 5-HTRs are expressed in both post-synaptic non-serotonergic neurons (referred to as heteroreceptors) and on serotonergic neurons themselves (referred to as autoreceptors). The two subpopulations make unique contributions to cell signaling, electrophysiology, and behavior, roles which are even sometimes opposing. 5-HT1A is the most well characterized 5-HTR in both physiological and behavioral function, and in understanding differences between its heteroreceptor and autoreceptor subpopulations. In vertebrate model organisms, 5-HT1A autoreceptors modulate emotion-related behaviors, but the contribution they make to behavior in Drosophila is unknown. Here we used RNAi to perform 5-HT1A knockdown and overexpression of 5-HT1A selectively in serotonergic neurons and found it disrupts a variety of behaviors at the larvae and adult stage, including locomotion, feeding, phototaxis, and circadian rhythm. This demonstrates that 5-HT1A autoreceptors make unique contributions to behavior in Drosophila, and provide robust readouts that can be used to examine the autoreceptor signaling pathways in serotonergic circuit function.

Disclosures: B. Potter: None. **A. Bell:** None. **H. Schneider:** None. **T. Fox:** None. **A. Urcuyo:** None. **M. Branch:** None. **I. Lamperti:** None. **E. Walker:** None. **A. Fernung:** None. **D.H. Roossien:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.08/I4

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

Support: NIH Grant R01DA047924

Title: Discovery of novel small molecules as allosteric ligands of the dopamine transporter as therapeutic agents for NeuroHIV

Authors: *C. E. AUGELLI-SZAFRAN[1], J. ZHU[3], O. MOUKHA-CHAFIQ[2];
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Abstract: Allosteric modulation of interaction between Dopamine Transporter (DAT) and HIV-1 transactivator of transcription (Tat) by small molecules suggests a potential therapeutic intervention for HIV-infected patients with concurrent cocaine abuse. We have previously reported *in vitro* and *in vivo* studies on a novel quinazoline allosteric modulator, **SRI-32743**, which was shown to attenuate Tat-induced inhibition of [^{3}H]DA uptake and decrease the cocaine-mediated dissociation of [^{3}H]WIN35,428 binding in CHO-K1 cells expressing hDAT. However, **SRI-32743** showed poor ADME (absorption, distribution, metabolism, and excretion) properties, including aqueous solubility (1.3 μM), metabolic stability in mouse and human liver microsomes (MLM $t_{1/2}$ = 6.9 min; HLM $t_{1/2}$ = 9.1 min), and low exposure in mouse plasma. This profile precludes the development of **SRI-32743** as a pre-clinical candidate. Hence, optimization was performed through various structural modifications to improve these properties. The cheminformatics software, Optibrium StarDrop™, was used to predict the solubility and metabolic stability of analogs of **SRI-32743**. In addition, *in silico* molecular docking in a human DAT homology model was adopted to study the ligand-protein interactions and provide insight into the design of analogs with improved potency. Our initial structure-activity relationship (SAR) campaign to improve the ADME properties of **SRI-32743** resulted in the discovery of **SRI-50141** which has a novel scaffold and an improved pharmacological profile ([^{3}H]WIN35,428 hDAT binding IC_{50} = 0.97 μM and [^{3}H]DA uptake IC_{50} = 0.59 μM) versus **SRI-32743** ([^{3}H]WIN35,428 hDAT binding IC_{50} = 4.6 μM and [^{3}H]DA uptake IC_{50} = 8.2 μM). A significant improvement of the metabolic stability was also observed for **SRI-50141** (MLM $t_{1/2}$ = 78 min, HLM $t_{1/2}$ = 258 min) versus **SRI-32743**, while its solubility (1 μM) needs further optimization. The SAR studies, including biological results and ADME properties, will be discussed. This work was supported by NIH grant R01DA047924.

Disclosures: C.E. Augelli-Szafran: None. **J. Zhu:** None. **O. Moukha-Chafiq:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.09/I5

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

Support: 1R01NS126454

Title: Using PEDOT/CNT Coated Microelectrode Arrays to Detect In Vivo 5-HT Release in the Basolateral Amygdala

Authors: *B. BOSTON[1], U. SIWAKOTI[2], A. SIGDEL[2], A. SWAVEY[4], D. KODROS[5], P. M. PITYCHOUTIS[6], E. CASTAGNOLA[3], B. J. KOLBER[7];
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Abstract: Pain is one of the most frequent causes for patients seeking clinical care. Many regions in the CNS are critical for processing nociception and pain. One of these areas, the basolateral amygdala (BLA) encodes motivational-affective behavior in the context of injury. Disruptive signaling in the BLA may contribute to the development and maintenance of chronic pain. In this study, we explored the role of serotonin (5-HT) in injury-induced changes in BLA signaling. 5-HT is known to increase excitability in the BLA after injury potentially contributing to pain-like changes. This effect makes treatment with selective serotonin reuptake inhibitors (SSRIs) challenging for pain patients as increases in 5-HT in the BLA may counteract beneficial effects of 5-HT in other brain regions. The full extent of 5-HT signaling in the BLA in the context of noxious injury and the development of chronic pain is unknown. To study 5-HT in the context of injury, we used square wave voltammetry (SWV) to measure 5-HT *in vivo* in the BLA two weeks after peripheral-nerve injury. We show validation of using poly(3,4-ethylenedioxythiophene)/carbon nanotube (PEDOT/CNT) coated SWV microelectrode probes with an optimized waveform for 5-HT to allow for sensitive detection of 5-HT both *in vivo* and *in vitro*. During recordings we found promising traces of 5-HT detection at 0.29V with differences between control mice and mice with spared nerve injury. These data measuring extracellular 5-HT release using SWV were compared to BLA tissue analysis of neurotransmitters using high performance liquid chromatography (HPLC). This shows the importance of analysis of extracellular 5-HT compared to total 5-HT levels. Overall, these preliminary findings will aid in better understanding serotonin dynamics in the BLA in the context of neuropathic injury.

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Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.10/I6

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

Title: Revisiting Dopamine Transporter Localization: Evidence for Intracellular DAT Expression

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Abstract: Dopamine (DA) is a critical neurotransmitter that regulates a wide range of physiological functions, including movement and emotion. Dopaminergic neurons are primarily located in the substantia nigra and ventral tegmental area, where they project to target regions such as the dorsal striatum, nucleus accumbens, and prefrontal cortex. Following its release into the extracellular space, DA binds to DA receptors to initiate intracellular signaling cascades. DA signaling is terminated primarily through reuptake by the DA transporter (DAT), a membrane protein responsible for regulating extracellular DA levels. Because of its central role in DA homeostasis, DAT is the target of numerous therapeutic and recreational drugs. Medications used to treat disorders such as attention-deficit/hyperactivity disorder (ADHD), as well as drugs of abuse such as cocaine, all increase extracellular DA levels by altering DAT function. However, despite acting through a similar mechanism, these compounds exhibit different therapeutic and addictive properties. This observation raises the possibility that DAT may possess functions beyond its established role. Therefore, the goal of this study was to investigate the potential intracellular localization of DAT and explore whether previously unrecognized intracellular functions may contribute to dopaminergic signaling. To address this question, two cellular models were utilized: HEK293 cells transfected with a DAT-FLAG construct and LUHMES cells differentiated into dopaminergic neurons. In HEK293 cells, multiple anti-DAT and anti-FLAG antibodies were used in combination with fluorescence microscopy to examine DAT localization. These studies revealed distinct intracellular punctate DAT labeling throughout the cell body. The specificity of this signal was supported by the absence of labeling in wild-type HEK293 cells and by co-localization studies using validated intracellular markers. To confirm these findings in a more physiologically relevant model, similar experiments were performed in differentiated LUHMES cells using multiple DAT antibodies. LUHMES cells also exhibited intracellular DAT labeling and co-localization with intracellular markers, supporting the presence of DAT within intracellular compartments. Future studies will focus on replicating these findings and defining the precise intracellular localization of DAT. Identifying the specific compartment(s) in which DAT resides will provide important insight into potential non-canonical functions of the transporter and may reveal novel mechanisms that contribute to dopaminergic signaling and drug action.

Disclosures: A. May: None. **B.E. Powers:** None. **M. Quiroz:** None. **G.E. Torres:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.11/I7

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

Title: Beyond Reuptake: Characterization of Intracellular Norepinephrine Transporter Localization

Authors: *A. G. UTLEY[1], B. POWERS[2], M. QUIROZ[3], G. E. TORRES[4];
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Abstract: Beyond Reuptake: Characterization of Intracellular Norepinephrine Transporter Localization
Abigail Utley, Brian Powers, Marisol Quiroz, and Gonzalo Torres
Department of Molecular Pharmacology and Neuroscience, Loyola University Chicago, Maywood, IL
Norepinephrine (NE) is a critical monoamine that acts as a neuromodulator in both the Central Nervous System (CNS) and the Peripheral Nervous System (PNS). In the CNS, NE is synthesized in a group of neurons within the pontine brainstem known as the locus coeruleus (LC). LC axons project widely throughout the brain and spinal cord to regulate arousal, mood, learning, and memory. Upon release into the synaptic and extracellular space by axon terminals and varicosities, NE acts by binding to nearby plasma membrane receptors and initiating downstream signaling responses. The primary mechanism regulating extracellular NE levels is reuptake through the norepinephrine transporter (NET). Interestingly, much of our understanding of NE function derives from the effects of drugs that target NET, including both therapeutic agents and drugs of abuse. Several selective norepinephrine reuptake inhibitors (NRIs) increase extracellular NE by blocking NET-mediated uptake. However, despite sharing a common mechanism of action, different NRIs are prescribed for distinct clinical conditions. For example, reboxetine is approved outside the United States for the treatment of major depressive disorder (MDD), whereas atomoxetine is primarily prescribed for attention-deficit/hyperactivity disorder (ADHD). While these observations reflect the diverse physiological roles of NE, they also raise the possibility that NE may have additional, non-canonical functions. Previous studies have suggested that other monoamines, including dopamine and serotonin, can participate in intracellular signaling processes. We therefore hypothesized that NET may be localized to intracellular compartments where it could facilitate NE transport and signaling. To examine NET localization, we performed immunocytochemistry in HEK293 cells transfected with a NET-FLAG construct. Using antibodies against NET and FLAG, we observed distinct intracellular NET-positive puncta in transfected cells. These findings were supported by the absence of staining in wild-type HEK293 cells and by co-labeling experiments using markers of intracellular and plasma membrane compartments. Future studies will investigate NET localization in endogenous cell lines and tissue models and will employ electron microscopy to further characterize its subcellular distribution.

Disclosures: A.G. Utley: None. **B. Powers:** None. **M. Quiroz:** None. **G.E. Torres:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.12/I8

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

Title: The Serotonin Transporter as a Novel G Protein-Regulated Signaling Protein

Authors: *C. M. WOOD[1], M. QUIROZ[2], G. E. TORRES, Sr.[3];
[1]Mol. Pharmacol. and Therapeut., Loyola Univ. Chicago Stritch Sch. of Med., Maywood, IL; [2]Loyola Univ., Maywood, IL; [3]Mol. Pharmacol. & Neurosci., Loyola Univ. Chicago SSOM, Chicago, IL

Abstract: Neuropsychiatric disorders such as anxiety and depression affect millions worldwide and remain a leading cause of disability. Although selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants, one-third of patients fail to achieve remission. SSRIs increase extracellular serotonin by blocking its reuptake through the serotonin transporter (SERT), yet they do not directly address deficits in serotonin release. Consequently, identifying mechanisms that regulate serotonin release may reveal novel therapeutic strategies for mood disorders. Serotonin-releasing agents such as MDMA, an amphetamine derivative, increase extracellular serotonin by promoting non-vesicular serotonin efflux through SERT. While MDMA has shown therapeutic potential, its neurotoxic and abuse-related liabilities limit widespread use. Therefore, elucidating the molecular mechanisms regulating SERT-mediated serotonin efflux may facilitate the development of safer and more effective serotonergic therapeutics. Emerging evidence indicates that heterotrimeric G proteins regulate monoamine transporter function. Previous studies from our laboratory demonstrated that G protein βγ (Gβγ) subunits directly interact with the dopamine transporter (DAT) and promote psychostimulant-induced dopamine efflux. Given the structural and functional similarities between DAT and SERT, we hypothesized that G proteins similarly regulate SERT activity. Using co-immunoprecipitation, we identified interactions between SERT and both Gβγ and Gα subunits. Preliminary findings further suggest that Gαi exhibits the strongest association with SERT, implicating Gαi-dependent signaling as a potential regulator of transporter function. Based on these observations, we propose two non-mutually exclusive mechanisms by which G proteins regulate SERT activity. First, activation of upstream G protein-coupled receptors may recruit Gαi signaling complexes to SERT, coupling transporter function to intracellular signaling pathways. Second, substrate or ligand binding may induce conformational changes in SERT that promote G protein recruitment. Ongoing biochemical, pharmacological, and computational studies are aimed at defining the molecular basis of these interactions and determining their contribution to serotonin efflux. Ultimately, these studies will establish a mechanistic framework for G protein-dependent regulation of SERT and enable structure-based virtual screening efforts to identify compounds that reproduce the therapeutic serotonin-releasing properties of MDMA while minimizing toxicity and abuse liability.

Disclosures: C.M. Wood: None. **M. Quiroz:** None. **G.E. Torres:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.13/J1

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

Support: NIH, NINDS, R01NS121014

Title: Investigating estrogen-mediated regulation of adenosine release in sleep circuitry

Authors: *P. DUBEY[1], J. VENTON[2];
[1]Chem., Univ. of Virginia, Charlottesville, VA; [2]Chem., Univ. of Virginia, Charlottesvle, VA

Abstract: Recent clinical and basic research have highlighted sex-differences in sleep, with women reporting lower sleep quality and higher occurrences of sleep disturbances than men. Adenosine, a major driver of sleep regulates the homeostatic need for sleep, or sleep pressure. Accumulation of adenosine in the brain during wakefulness increases sleep pressure, which is relieved during sleep with its clearance. Elevated sleep pressure increases activity in key sleep nuclei, including the median preoptic (MnPO) and ventrolateral preoptic (VLPO), while inhibiting wake-promoting nuclei such as the basal forebrain and locus coeruleus, thereby promoting sleep. Conversely, wakefulness is characterized by activation of wake centers and inhibition of sleep centers, resulting in sustained wakefulness. Adenosine, via its receptors, modulates this sleep-wake switch. Thus, sex differences in adenosine dynamics could underlie the hormone-sensitive sleep issues in women. Here, we show distinctions in adenosine neurotransmission in male and female rats in MnPO and VLPO as well as estrogen-mediated differences in adenosine dynamics within MnPO and VLPO. We monitored rapid changes in extrasynaptic adenosine using fast-scan cyclic voltammetry (FSCV) in MnPO and VLPO on a sub-second timescale, providing spatial and temporal resolution that has not been possible with traditional methods of investigating adenosine. Our results show significantly higher adenosine release concentration in both, MnPO and VLPO in females than males. The elimination of ovarian hormones resulted in significant reduction of adenosine release concentration and frequency as compared to ovariectomized females that were administered estradiol (E2) to mimic proestrus in MnPO. In contrast, we observed no significant differences between the two groups in adenosine concentration in VLPO. Additionally, we observed significantly higher release frequency in VLPO in ovariectomized females as compared to those administered E2. Lastly, we also demonstrate that estrogen sensitivity of adenosine release in MnPO is mediated by estrogen receptor α (ERα). Our observations not only demonstrate that adenosine dynamics with MnPO and VLPO are sensitive to steroid hormones but also show that the MnPO is a key site for estrogen-mediated changes in adenosine release that are regulated via ERα.

Disclosures: P. Dubey: None. **J. Venton:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.14/J2

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

Title: Gut Brain Interactions: Campylobacter jejuni-induced neurotransmitter alterations in the brain

Authors: *A. PALANIYAPPAN[1], A. MURUGAN[1], Y.-J. CHUANG[1], P. S. MOHANKUMAR[1], L. S. MANSFIELD[2], S. M. MOHANKUMAR[1];
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Abstract: *Campylobacter jejuni (C. jejuni)* is a leading cause of bacterial gastroenteritis and is strongly associated with Guillain-Barre syndrome (GBS). GBS is often accompanied by neuroendocrine, autonomic, and behavioral disturbances. Although previous studies have shown that *C. jejuni* infection induces anxiety-like behavior in rodents, the underlying mechanisms remain unclear. We hypothesized that *C. jejuni* infection alters monoamine neurotransmitter levels in brain regions involved in behavioral and neuroendocrine regulation. In the current study, adult male C57BL/6 mice were orally inoculated with trypticase soy broth (Vehicle/ Control), a wild type *C. jejuni* strain (11168), a 11168 knockout strain, or a 11168 complemented strain. Thirty days after infection, animals were sacrificed, Gastrointestinal (GI) tissues were preserved in formalin and brains were frozen and stored at -80°C . The GI tissues were examined for gross pathology. In the frozen brain, paraventricular nucleus (PVN), bed nucleus of the stria terminalis (BNST), central amygdala (CeA), and motor cortex were analyzed for monoamines such as norepinephrine (NE), dopamine (DA), and serotonin (5-HT) concentrations using high-performance liquid chromatography with electrochemical detection (HPLC-EC). Mice infected with wild-type *C .jejuni* exhibited mild to severe GI pathology with a significant increase in DA levels within the CeA. NE and 5-HT were elevated in the CeA but was not significant on statistical analysis. No significant changes in neurotransmitter levels were seen in other brain areas monitored. Mice infected with KO strain did not show any GI pathology or neurotransmitter changes in the brain regions examined. Interestingly, mice infected with the complemented strain exhibited gastrointestinal pathology but failed to show similar neurochemical alterations. These findings demonstrate that *C. jejuni* selectively modifies monoaminergic signaling in the central amygdala, a key brain region involved in emotional and stress-related responses. The dissociation between GI pathology and neurotransmitter changes suggests that specific gut-brain signaling mechanisms, rather than gut pathology alone, may contribute to infection-induced behavioral and neuroendocrine alterations.

Disclosures: A. Palaniyappan: None. **A. Murugan:** None. **Y. Chuang:** None. **P.S. Mohankumar:** None. **L.S. Mansfield:** None. **S.M. Mohankumar:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.15/J3

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

Title: Impact of prenatal EDC exposure followed by postnatal ozone inhalation on neurotransmitter levels in the Paraventricular nucleus.

Authors: *T. SELVARAJ[1], N. RIVERA-RIOS[5], Y.-J. CHUANG[2], R. LEWANDOWSKI[5], J. WAGNER[5], P. S. MOHANKUMAR[3], S. M. MOHANKUMAR[4];
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Abstract: Exposure to the plasticizing endocrine disrupting chemicals (EDCs), such as bisphenol A (BPA) and diethyl hexyl phthalate (DEHP) is widespread and pernicious. We have previously shown that prenatal exposure to low doses of these chemicals alone or in combination can have deleterious effects on the offspring by inducing "programming" of cellular processes leading to adult-onset disorders such as metabolic dysfunction and hypertension. Atmospheric ozone is another pervasive environmental pollutant generated by industrial and vehicular emissions, that results in widespread human exposure. Ozone exposure can cause inflammation of the airways. While the impact of prenatal EDC exposure and ozone exposure in adulthood have been studied independently, there are no studies that have combined these two exposures. In this study, we investigated the impact of a combination of prenatal and adult exposures on the stress axis, specifically neurotransmitter changes in the paraventricular nucleus (PVN) of the hypothalamus since it is a key site for stress axis activation. Pregnant Sprague-Dawley (SD) rats were orally exposed to BPA at a dose of 5 ug/kg body weight (BW), DEHP at a dose of 7.5 mg/kg BW, or both BPA and DEHP from Day 6 to Day 21 of gestation. When the male offspring reached adulthood, they were exposed to 0.6 ppm ozone or air for 4 days in a controlled chamber. Animals were sacrificed on the 5th day, their brains were harvested, frozen and sectioned. The PVN was micro dissected and analyzed for monoamine levels using HPLC-EC. Analysis revealed elevated levels of norepinephrine (NE) in offspring following ozone exposure relative to air-exposed controls. Furthermore, a significant increase in NE levels was observed in offspring subjected to combined prenatal BPA and postnatal ozone exposure. These findings suggest that secondary environmental insults, such as postnatal ozone inhalation, may exacerbate the physiological stress response in rats with prior prenatal exposure to EDCs

Disclosures: T. Selvaraj: None. **N. Rivera-Rios:** None. **Y. Chuang:** None. **R. Lewandowski:** None. **J. Wagner:** None. **P.S. Mohankumar:** None. **S.M. Mohankumar:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.16/J4

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

Title: Identification of an evolutionarily conserved intronic enhancer regulating expression of the norepinephrine synthesis enzyme dopamine β-hydroxylase

Authors: *M. BALDY[1,2], E. WANG[3], N. PLUMMER[4], P. WADE[5], I. EVSYUKOVA[4], P. JENSEN[4];
[1]Natl. Inst. of Envrn. Hlth. Sci., Durham, NC; [2]Pharmacol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Washington Univ. in St. Louis, SAINT LOUIS, MO; [4]Neurobio. Lab, NIEHS/NIH, Durham, NC; [5]Epigenetics & RNA Biol. Laboratory, NIEHS/NIH, Durham, NC

Abstract: The critical catecholamine norepinephrine (NE) is produced by small populations of noradrenergic cells located in the brainstem, sympathetic chain, and adrenal medulla. Despite their limited numbers, these cells have an outsized impact on diverse behaviors and physiological drives, including arousal, stress responses, and autonomic function. Dysregulation of NE synthesis in the locus coeruleus, the largest population of noradrenergic neurons in the brain, has been implicated in numerous psychiatric, neurodevelopmental, and neurodegenerative disorders, highlighting the importance of understanding the regulation of NE synthesis. Identifying factors that contribute to variations in NE levels are crucial for identifying vulnerabilities to neurological disorders and may reveal novel therapeutic targets. The enzyme responsible for the final step in NE synthesis is dopamine β-hydroxylase, encoded by the *DBH* gene, which catalyzes the conversion of dopamine to NE. Our lab generated a floxed allele of mouse *Dbh* which unexpectedly exhibited reduced *Dbh* mRNA levels in both central and peripheral noradrenergic cells in the absence of Cre recombination. NE was also reduced in the brain, but not in the adrenal medulla or plasma. Sequence analysis indicates that the insertion of a loxP site in intron 1 of *Dbh* interrupted an evolutionarily conserved sequence element located within a larger putative enhancer that is present in both mouse and human *DBH* genes. We employed CRISPR interference (CRISPRi) and ATAC-seq in *Dbh*-expressing mouse neuroblastoma cells to assess the activity of this putative enhancer region and further characterize its capacity to regulate *Dbh* transcription. We found that CRISPRi of sequences within the conserved region significantly decreased *Dbh* and induced a closed chromatin conformation at the target site. Similar targeting of the orthologous region in human neuroblastoma cells significantly reduced *DBH* mRNA and protein expression, demonstrating an evolutionarily conserved role for this enhancer in regulating DBH expression. Together, these findings identify a conserved genetic regulatory element that influences DBH expression and may contribute to individual variation in NE synthesis. Ongoing studies are investigating the functional consequences of enhancer perturbation on NE production, the broader chromatin landscape and transcriptional networks influenced by this regulatory element, and the capacity of enhancer activation to increase DBH expression. Future work will also examine whether known genetic variants within this conserved region alter DBH expression and contribute to altered NE synthesis.

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Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.17/J5

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

Support: NIH
NSF

Title: Mechanistic insights into VAChT-mediated ACh release in Drosophila

Authors: *R. A. NEMAT, H. O. LAWAL;
Delaware Ctr. for Neurosci. Research, Dept. of Biol. Sci., Delaware State Univ., Dover, DE

Abstract: Cholinergic synaptic transmission is required for mundane yet essential functions such as locomotion and cognition. ACh signaling can also be viewed in the context of Alzheimer's disease, where degeneration of cholinergic neurons and reduced cholinergic neurotransmission contribute significantly to cognitive decline and memory impairment. Therefore, understanding the mechanisms that regulate acetylcholine synthesis, packaging, and release may provide valuable insights into the development of Alzheimer's disease and help identify new strategies. To develop better interventions, it is important to understand the molecular mechanisms underlying neuronal loss in cholinergic systems. The neurotransmitter acetylcholine (ACh) plays a central role in regulating vital neurological processes, such as cognition. As a result, increases or decreases in neuronal cholinergic signaling impair learning and memory. Although much about how acetylcholine is regulated is known, the mechanism through which alterations in cholinergic signaling affect changes in ACh-linked behavior is not fully understood. Importantly, the nature of the relationship between vesicular acetylcholine packaging and its release at the synaptic cleft is also unclear. In this study, we investigated how altered VAChT expression affects its localization at cholinergic active zones, brain *ACh* levels, and neurotransmitter homeostasis in the adult *Drosophila* brain. We report that *VAChT* overexpression increased acetylchone (*ACh*) levels and its localization at synaptic release sites, while *Vacht* mutant flies showed significant reduction in Ach levels. Choline levels were elevated in *VAChT* overexpresions but unchanged in mutants. These results demonstrate that *VAChT* directly regulates *ACh* storage and release in the Drosophila brain. Ongoing work in the lab seeks to apply these techniques and findings to understand the effect of AB-42 on cholinergic signaling. Together, these studies provide mechanistic insights into cholinergic dysfunction associated with normal aging, with implication for AD-related pathology.

Disclosures: R.A. Nemat: None. **H.O. Lawal:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

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Program #/Poster #: PSTR343.18/J6

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

Support: NIH, NINDS, R01NS121014

Title: mGluR5 bidirectionally regulates glutamate and adenosine at Schaeffer collateral-CA1 synapses in the mouse ventral hippocampus

Authors: *D. SURENDRAN[1], J. VENTON[2];
[1]Chem., Univ. of Virginia, Charlottesville, VA; [2]Chem., Univ. of Virginia, Charlottesvle, VA

Abstract: Adenosine is a major neuromodulator involved in hippocampal synaptic transmission. It exerts opposing effects through the inhibitory A1 (A1R) and facilitatory A2A (A2AR) receptors. High-frequency glutamatergic activity is known to drive extracellular adenosine accumulation. However, the specific receptor-mediated mechanisms that couple excitatory neurotransmission to adenosine feedback is yet poorly understood. In this study, we employed a multiplexed approach to simultaneously measure stimulated adenosine release using fast scan cyclic voltammetry (FSCV) and its effect on glutamate neurotransmission using iGluSnFR fluorescence imaging at Schaeffer collateral (SC)-Cornu Ammonis 1 (CA1) synapses in the mouse ventral hippocampus. We investigated the contributions of ionotropic glutamate receptors (AMPAR and NMDAR), the group I metabotropic glutamate receptor mGluR5, and adenosine receptor subtypes (A1R and A2AR) to neurotransmitter dynamics at SC-CA1 synapses using pharmacological tools and adenosine receptor knockout mice. Our results indicate that neither AMPAR nor NMDAR blockade alone alters adenosine levels, establishing that ionotropic receptors do not regulate adenosine accumulation. However, pharmacological blockade of mGluR5 receptors significantly reduced glutamate release but increased extracellular adenosine levels. This shows a novel compensatory mechanism in which adenosine tone increases when mGluR5 signaling is suppressed. Further studies demonstrated that A1R normally sustains a self-reinforcing loop of inhibitory control and adenosine availability. While A2AR activation facilitated glutamate release by decreasing A1R inhibition, A2AR deficiency did not alter the constitutive adenosine pools. This finding confirms the primary role of adenosine in the modulation of plasticity. Our findings define a hierarchically organized regulatory network in which mGluR5 functions as a crucial link between glutamatergic transmission to adenosine homeostasis. This mGluR5–adenosine axis provides essential metaplastic control in the ventral CA1 and represents a promising therapeutic target for disorders characterized by synaptic dysregulation, such as Alzheimer's disease and affective disorders.

Disclosures: D. Surendran: None. **J. Venton:** None.

Poster

PSTR343: Neurotransmitters

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.19/J7

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

Title: Bisphenol A and 17-beta-estradiol regulate GLAST/EAAT1in cultured Bergmann Glia

Authors: *L. C. HERNANDEZ[1], N. MORALES-RAMÍREZ[1], E. CALDERON-ARANDA[1], A. ORTEGA[1], F. CASTELÁN[2];
[1]Toxicología, Cinvestav-IPN, Mexico City, Mexico; [2]Inst. de Investigaciones Biomedicas, UNAM, Tlaxcala, Mexico

Abstract: Glutamate (Glu) is the major excitatory neurotransmitter within the central nervous system (CNS). The clearance of Glu from the synaptic cleft is efficiently carried out by glial Glu transporters belonging to the Excitatory Amino Acid Transporter (EAAT) family. The activity of these transporters is fundamental in order to prevent an excitotoxic insult due to an overstimulation of Glu receptors that would result in neuronal death. In the cerebellum, Bergmann glial cells play a critical role in cerebellar plasticity, these cells express exclusively the GLAST/EAAT1 subtype of glia Glu transporters and completely enwrap the most abundant glutamatergic synapse in the CNS: the one established between parallel fibers (PF) and Purkinje cells (Pc) in the cerebellar molecular layer. Consequently, it is not surprising that the plasma membrane abundance and function of Glu transporters are tightly regulated at the transcriptional, translational, and post-translational levels. In the cerebellar cortex, neuroactive molecules like estrogens have been widely recognized as neuroprotective agents acting through both nuclear and plasma membrane receptors. In fact, 17-b- estradiol is synthesized locally in Purkinje and granular cells. Using a well-characterized culture of chick cerebellar Bergmann glia cells, we analyzed the effects of the exposure of cultured Bergmann glia cells to Bisphenol A (BPA)—an estrogen-like pollutant and endocrine disruptor— and to 17-b- estradiol on the Glu uptake activity. A time- and dose-dependent increase in Glu uptake activity, was detected *via* a [^{3}H] D-aspartate assay. A Western blot approach was used to detect the expression of estrogen receptors and aromatase, the rate-limiting enzyme in local estrogen biosynthesis. Interstingly, BPA exposure augmented estrogen receptors expression in a time- and dose-dependent manner. These results will be discussed in terms of glial cell vulnerability and Glu transport involvement in the deleterious effects of the endocrine disruptor BPA.

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Poster

PSTR343: Neurotransmitters

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

Support: NIH/NIDA Grant R01DA056547
SUNY Research Seed Grant Award (RFP#23-01-RSG)
NIH R01DA062090

Title: Differential catecholamine changes during methamphetamine incubation: an in vivo voltammetry assessment in the nucleus accumbens and bed nucleus of the stria terminalis

Authors: *R. BHIMANI[1], J. PARK[2];
[1]Univ. At Buffalo, Buffalo, NY; [2]university at buffalo-SUNY, buffalo, NY

Abstract: The craving for methamphetamine (METH) often intensifies during prolonged abstinence, a phenomenon known as the incubation of drug craving. While the nucleus accumbens (NAc) dopamine (DA) system is heavily implicated in reward and drug-seeking, the often overshadowed bed nucleus of the stria terminalis (BNST) norepinephrine (NE) system plays a critical role in stress-induced relapse; however, the real-time dynamics of these limbic brain regions during incubation remain to be elucidated. To investigate this, rats were trained to self-administer METH (0.05 mg/kg/inf) during daily 3-hour sessions for 28 days, followed by forced abstinence. Rats were assigned to either an early abstinence group (Withdrawal Day 2) or a late abstinence group (Withdrawal Day 28), at which point they were anesthetized with urethane for *in vivo* fast-scan cyclic voltammetry (FSCV) recordings to investigate changes in DA and NE regulatory mechanisms. Through pharmacological, anatomical, and electrochemical evidence, we highlight distinct changes in DA and NE signaling in METH and Saline administering rats. Together, these findings demonstrate that the incubation of METH craving is accompanied by time-dependent, region-specific shifts in neurotransmission that may underlie relapse to drug seeking following abstinence.

Disclosures: R. Bhimani: None. **J. Park:** None.

Poster

PSTR343: Neurotransmitters

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

Support: NIH Grant NS129675
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Title: Differentiation and agonist treatment increase cds1 and D_5dopamine receptor expression in SH-SY5Y human neuroblastoma cells

Authors: S. METKAR[1], **T. ADEGBENRO**[1], N. ONUOHA[2], *A. S. UNDIEH[1];
[1]CUNY Sch. of Med., New York, NY; [2]MCBS, CUNY Sch. of Med., NY, NY

Abstract: CDS1 catalyzes the synthesis of CDP-diacylglycerol and thus regulates the rate-limiting step in phosphatidylinositide (PI) signaling. The polyphosphorylated derivative of PI, PI-4,5-bisphosphate (PIP2) is required for phospholipase C as well as PI-3-kinase signaling cascades. Given the widespread utilization of these signaling systems among G-protein-coupled and neurotrophic factor receptors, cellular PIP2 availability could serve as a critical determinant

of diverse CNS functions including neurotrophic control of neurogenesis, neuroresilience, and neuroregeneration. While neurotrophins are classical modulators of PI-3-kinase signaling, recent work from this lab demonstrated the involvement of dopamine, acting via the D_5 receptor, in neural CDS1-dependent CDP-diacylglycerol signaling. The current work focuses on how neurotrophin (BDNF)-driven cellular differentiation or pre-exposure to a dopamine agonist could modulate the gene and protein expression of the D_5 receptor or CDS1 in proliferating or differentiated SH-SY5Y cells. Using RT-qPCR and immunofluorescence techniques to study gene and protein expression, we observed extremely low expression of cds1 mRNA in proliferating undifferentiated SH-SY5Y cells. Conversely, CDS1 expression was induced several fold in differentiating SH-SY5Y cells. Confocal microscopy studies showed that CDS1 protein similarly increased in differentiated SH-SY5Y cells or following exposure to the dopamine agonist SKF38393. Surprisingly, SKF38393 treatment also concentration-dependently increased cellular D_5 receptor protein, and most of the receptor expression was preferentially colocalized to the endoplasmic reticulum. Taken together, these observations imply that neurotrophic differentiating agents or SKF38393 could induce the expression of the D_5 receptor and its downstream mediator, CDS1, thus providing a potential mechanism for upstream regulation of PI-dependent signaling cascades. Upcoming studies will explore the relevance of these findings to neurotrophic signaling broadly and specifically neuroresilience mechanisms.

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Poster

PSTR343: Neurotransmitters

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

Support: BBSRC BB/S003894
EXC-2049-390688087-NeuroCure

Title: iGlu3Fast and iGlu3Slow, fluorescent reporters for detection of spontaneous glutamate activity in the brain

Authors: O. TRAN[1], S. BERTELLI[2], H. J. HUGHES[4], A. J. R. PLESTED[3], ***K. TÖRÖK**[4]; [1]City St George's, Univ. of London, London, United Kingdom; [2]Cluster of Excellence NeuroCure, Humboldt Univ., Berlin, United Kingdom; [3]Cluster of Excellence NeuroCure, Humboldt Univ., Berlin, Germany; [4]City St George's, Univ. of London, London, United Kingdom

Abstract: When designing and applying biosensors, it is critical that the sensor properties, e.g. affinity, kinetics, sensitivity are considered taking into account the characteristics of the phenomenon to be observed, e.g. the ligand concentrations, the time scale and amplitude of events. For monitoring neurotransmission with high spatial and temporal resolution, fast

response kinetics and high sensitivity are optimal, however, for tracking large-scale events, it is desirable that the signal detection is more prolonged. Here, we report variants of the iGluSnFR3 glutamate sensor with ultrafast (iGlu3Fast) and super-slow (iGlu3Slow1 and iGlu3Slow2) response kinetics and large fluorescence dynamic ranges both in solution and in situ. Monitoring spontaneous activity, the measured rise times (10-90%) extracted from the raw traces for the sensors expressed in organotypic hippocampal slices 19 ± 13 ms (iGlu3Fast $n = 47$) and 110 ± 140 ms (iGlu3slow1, $n = 39$). Decay time constants for spontaneous glutamate transients (τ) were 19 ± 11 ms (iGlu3Fast, $n = 42$) and 440 ± 420 ms (iGlu3Slow2, $n = 45$). The maximum dynamic ranges ($\Delta F/F_{0\ max}$) measured for iGlu3Fast and iGlu3Slow2 were 4.4 ± 2 ($n = 28$) and 6.9 ± 6.7 ($n = 34$), respectively. Strikingly, different kinds of glutamate transient were revealed when spontaneous glutamate release activity was monitored by two-photon imaging of in hippocampal organotypic slices: the ultrafast sensor detected localised glutamate release events while the super-slow-decay sensor reported global events. Thus, the rapid kinetics and increased fluorescence dynamic range make iGlu3Fast an excellent candidate for imaging high-frequency glutamate release at synapses while iGlu3Slow2 has the potential for mesoscale imaging of brain activity to record global events with high sensitivity.

Disclosures: O. Tran: None. **S. Bertelli:** None. **H.J. Hughes:** None. **A.J.R. Plested:** None. **K. Török:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.01/K3

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01NS117372
NIH Grant R21NS121284
National Science Foundation Career Award 2440057

Title: Drosophila Neuroglian Is Required for Retrograde Signaling During Homeostatic Control of Synaptic Transmission

Authors: *Y. XIE[1], Y. CAI[1], B. HU[2], S. VICINI[1,3], T. WANG[1,3];
[1]Dept. of Pharmacol. and Physiol., [2]Dept. of Human Science, Sch. of Hlth., Georgetown Univ., Washington, DC; [3]Interdisciplinary Program in Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Homeostatic modulation of synaptic transmission is a conserved mechanism that stabilizes neural activity in response to perturbations such as toxins, genetic mutations, or disease states. At synapses, presynaptic neurotransmitter release can be adjusted to maintain synaptic output within a stable physiological range. Disruption of this process can lead to circuit hyperexcitability or hypoexcitability and has been linked to neurological disorders including

epilepsy, schizophrenia, autism spectrum disorder, and neurodegeneration. Although retrograde signals from postsynaptic to presynaptic compartments are essential for synaptic homeostasis, the molecular mechanisms that transmit these signals across the synapse remain poorly understood. The Drosophila neuromuscular junction, a glutamatergic synapse, is a powerful model for identifying genes required for synaptic homeostasis. We previously showed that α2δ-3, an auxiliary subunit of voltage-gated calcium channels, is required for presynaptic homeostatic plasticity by promoting the homeostatic potentiation of presynaptic calcium influx. Because α2δ-3 is positioned on the extracellular face of presynaptic release sites, it is well suited to receive and relay transsynaptic signals that regulate calcium channel function. Here, we identified Drosophila Neuroglian, a cell adhesion molecule and homologue of vertebrate L1-CAM, as a candidate binding partner of α2δ-3 through a mass spectrometry-based biochemical screen. Neuroglian is expressed as tissue-specific splice isoforms, including the neuronal isoform Nrg180 and the non-neuronal isoform Nrg167. Electrophysiological studies indicate that Nrg167, but not Nrg180, is required for presynaptic homeostatic plasticity. Biochemical experiments support a physical interaction between Neuroglian and α2δ-3, and confocal and super-resolution imaging suggest that postsynaptic Nrg167 regulates presynaptic α2δ-3 localization at active zones during homeostatic plasticity. Together, these findings support a model in which postsynaptic Nrg167 and presynaptic α2δ-3 form a transsynaptic signaling mechanism that enables retrograde communication during homeostatic control of synaptic transmission. This work identifies Neuroglian as a key regulator of synaptic stability and provides insight into conserved molecular mechanisms that may be disrupted in neurological disease.

Disclosures: Y. Xie: None. **Y. Cai:** None. **B. Hu:** None. **S. Vicini:** None. **T. Wang:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.02/K4

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01NS117372 (T.T.W.)
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NIH NRSA predoctoral fellowship F31NS139658 (Y.C.)

Title: Drosophila Chd1-Dependent Signaling Network Stabilizes Synapses Through Homeostatic Plasticity

Authors: *J. WANG[1], T. CUI[1], Y. CAI[1], D. MORENCY[2], R. NOKKU[3], R. HUANG[4], G. CHU[3], S. VICINI[1], T. WANG[1,2];
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Abstract: Autism spectrum disorder (ASD) is a prevalent neurodevelopmental disorder associated with mutations in many genes, including *CHD2*, an epigenetic regulator linked to chromatin remodeling and neural development. In *Drosophila*, the *CHD2* homologue *Chd1* is required for presynaptic homeostatic potentiation (PHP), an evolutionarily conserved form of synaptic plasticity that stabilizes synaptic strength following impaired postsynaptic receptor function. Although previous studies suggest that *Chd1* is essential for PHP, the downstream molecular pathways that mediate this effect remain poorly understood. Here, we investigated *Cadherin 74a* (*Cad74a*), a direct transcriptional target of *Chd1*, as a candidate regulator of synaptic homeostasis. Sharp-electrode electrophysiological recordings at the *Drosophila* neuromuscular junction revealed that *Cad74a* null mutants completely block both acute and chronic PHP. Genetic interaction experiments further demonstrated that *Cad74a* functionally interacts with *Chd1*, supporting a shared regulatory pathway. To determine whether additional *Chd1* downstream targets contribute to this process, we examined genes encoding extracellular matrix-associated molecules. Loss of *Trol*, *Kon*, or *Dlp* also produced a complete block of acute PHP, indicating that multiple *Chd1*-regulated effectors converge on a common pathway required for homeostatic synaptic plasticity. Together, these findings identify *Cad74a*, *Trol*, *Kon*, and *Dlp* as critical downstream effectors of *Chd1* in the control of synaptic homeostasis. Our results define a *Chd1*-dependent genetic network that is required for PHP and suggest that disruption of extracellular and synaptic signaling pathways may contribute to synaptic instability in *CHD2*-associated disorders.

Disclosures: J. Wang: None. **T. Cui:** None. **Y. Cai:** None. **D. Morency:** None. **R. Nokku:** None. **R. Huang:** None. **G. Chu:** None. **S. Vicini:** None. **T. Wang:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.03/K5

Topic: B.05. Synaptic Plasticity

Support: NIH R01 Award NS136753
NIH R01 Award NS130108

Title: The scaffolding protein Veli/Dlin7 regulates presynaptic homeostatic potentiation at the fly neuromuscular junction.

Authors: *M. BENDALE, C. FRANK;
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Abstract: To maintain neuronal stability, synapses must sustain steady neurotransmitter release. When disruptions occur, the brain uses a built-in balancing act called homeostatic plasticity, allowing the synapses to self-regulate and preserve steady activity. At the glutamatergic neuromuscular junction (NMJ) of Drosophila melanogaster, synapses show a resilient homeostatic response to altered excitability. This stabilization relies on presynaptic homeostatic potentiation (PHP), a core neurophysiological process that increases neurotransmitter release to counteract reduced postsynaptic receptor sensitivity. PHP is vital for synaptic plasticity, circuit stability, and network balance. At the fly NMJ, scaffolding protein Dlin-7/Veli plays an essential role in organizing postsynaptic glutamate receptor complexes and associated proteins, thereby supporting synapse formation and receptor clustering. Despite its importance in postsynaptic architecture, the contribution of Dlin-7/Veli to homeostatic signaling remains untested. In this study, we combined transgenic RNA interference with electrophysiological recordings at the Drosophila NMJ to examine the function of Dlin-7/Veli in PHP. We found that disruption of Dlin-7/Veli at the fly NMJ does not alter baseline neurotransmission. However, when homeostatic signaling was challenged by genetic ablation of a glutamate receptor subunit, loss of Dlin-7/Veli resulted in a failure of PHP. Morphological studies revealed that loss of Dlin-7/Veli in combination with homeostatic challenge exhibited an overgrowth of presynaptic terminal boutons. Additionally, by immunostaining, Dlin7/Veli deletion during homeostatic challenge displayed an abnormal diffusion of synaptic vesicles, as well as active zone defects. Together, these findings identified a new role for Dlin-7/Veli in regulation of PHP. Exploring the mechanisms by which Dlin-7/Veli gates PHP will help us reveal how neurons maintain reliable communication. Broadly, this type of information could shed light on how to approach neurological disorders driven by synaptic failure.

Disclosures: M. Bendale: None. **C. Frank:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.04/K6

Topic: B.05. Synaptic Plasticity

Support: PAPIIT IN228726

Title: Freely moving LTP in the Insular Cortex modulates taste recognition memory.

Authors: *G. RAMIREZ CASQUERA, student[1], M. LÓPEZ HERNÁNDEZ[2], L. F. RODRIGUEZ-DURAN[3], F. BERMUDEZ-RATTONI[4];
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Abstract: The projection from the basolateral amygdala (BLA) to the insular cortex (IC) constitutes a fundamental pathway for the integration of sensory, emotional, and motivational information involved in taste learning and feeding-related decision-making. Also, BLA-IC projection is implicated in taste aversion formation. Although synaptic plasticity within this circuit has been implicated in the formation of taste memories, direct demonstrations of long-term potentiation (LTP) in freely moving animals remain scarce. In the present study, we investigated whether in vivo LTP induced in the BLA-IC pathway of freely moving C57BL/6 mice modulates the recognition and evaluation of a novel tastant. To this end, animals were implanted with stimulating and recording electrodes targeting the BLA and IC, respectively, and robust LTP was induced using a high-frequency tetanization protocol (100 Hz) while the animals remained awake and freely moving. The behavioral consequences of synaptic strengthening were assessed using taste-exposure paradigms with low concentrations of quinine, analyzing both total consumption and the microstructure of ingestive behavior. Our results demonstrate that stable LTP can be successfully induced and maintained in the BLA-IC projection, producing a long-lasting increase in synaptic efficacy within a circuit that is critical for gustatory processing under physiologically relevant conditions. Importantly, this study provides one of the first demonstrations that stable in vivo LTP in the BLA-IC pathway of freely moving mice is sufficient to alter the earliest stages of novel taste evaluation. Although LTP did not significantly modify total consumption or overall ingestion patterns, it selectively affected the initial stages of taste processing. These findings suggest that synaptic potentiation in the BLA-IC pathway promotes faster and more precise discrimination of novel gustatory information rather than producing global changes in motivation or consumption.

Disclosures: G. Ramirez Casquera: None. **M. López Hernández:** None. **L.F. Rodriguez-Duran:** None. **F. Bermudez-Rattoni:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.05/K7

Topic: B.05. Synaptic Plasticity

Support: CRC 1315 project A11 DFG

Title: Connectomic analysis reveals organizing principles of mitochondrial cristae architecture

Authors: *S. HÜRKEY[1], G. SAGER[2], P. PFEIFFER[1], M. LEIGHTON[2], D. CLARK[2], S. SCHREIBER[1];
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Abstract: Neuronal mitochondria support energy production and calcium handling through processes that depend on both their cellular localization and the structure of their cristae-forming inner membrane. Recent connectome-scale studies have shown that mitochondria are positioned with micron-scale precision relative to synaptic and structural features, with systematic differences across neuron types, compartments, and activity states (Sager et al., 2025). However, while mitochondrial placement within neurons has begun to be understood, far less is known about how the internal membrane architecture of mitochondria is organized across neuronal circuits. Because cristae house the molecular machinery underlying oxidative phosphorylation, variation in cristae density and organization may reflect local energetic and biosynthetic demands that differ across neuronal compartments, synapses, and sites of long-term plasticity. To quantify mitochondrial membrane architecture at scale, we developed an automated approach for segmenting mitochondrial outer membranes and cristae from volumetric electron microscopy data. We applied these methods to the Drosophila hemibrain dataset, a high-resolution connectomic volume containing ~3.6 million mitochondria distributed across thousands of segmented and annotated neurons. Automated cristae segmentations closely matched human annotations (F1 = 0.82), enabling large-scale analysis of mitochondrial ultrastructure across neuron types and subcellular compartments. Across this dataset, mitochondrial membrane surface area, cristae membrane surface area, and cristae volume followed robust scaling relationships spanning a wide range of mitochondrial sizes. These analyses reveal how inner membrane architecture changes with mitochondrial size and establish quantitative scaling principles governing mitochondrial ultrastructure. We further examined how mitochondrial context contributes to variation in cristae organization, including differences across neuronal compartments and between mitochondria associated with pre- and postsynaptic regions. Together, these results provide a quantitative framework for studying mitochondrial ultrastructure at connectome scale and reveal systematic relationships linking cristae architecture, mitochondrial size, and neuronal context.

Disclosures: S. Hürkey: None. **G. Sager:** None. **P. Pfeiffer:** None. **M. Leighton:** None. **D. Clark:** None. **S. Schreiber:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.06/K8

Topic: B.05. Synaptic Plasticity

Support: NS085164
NS130108
NS136753

Title: How phasic and tonic motor neurons execute presynaptic homeostatic potentiation: distinct mechanisms using intracellular calcium and metabolic energy

Authors: *B. MALLIK[1], C. FRANK[2];
[1]Anat. and Cell Biol., Univ. of Iowa, IOWA CITY, IA; [2]Anat. and Cell Biol., Univ. of Iowa, Iowa City, IA

Abstract: Presynaptic homeostatic potentiation (PHP) maintains stable synaptic transmission at neuromuscular junctions (NMJs). PHP occurs after impairment of postsynaptic neurotransmitter receptors. Homeostatic signaling offsets the receptor challenge by potentiating neurotransmission from motor neurons. At *Drosophila* NMJs, phasic MN-Is and tonic MN-Ib motor neurons both possess the capacity to express PHP. Recent work shows that they perform this task in different ways. Phasic motor neurons are needed for "acute PHP," responding to short-term challenges like NMJ application of the glutamate receptor inhibitor philanthotoxin (PhTx, 15 min). By contrast, both kinds of motor neuron are needed if there is a chronic challenge, like glutamate receptor loss ("chronic PHP"). Our current work sheds some mechanistic light on how these distinct motor neuron types execute PHP.
We previously identified roles in PHP for ER-localized Ca^{2+} signaling channels like IP_3 receptors (IP_3R) and ryanodine receptors (RyR). Here we examined how intracellular Ca^{2+} signaling works in MN-Is vs. MN-Ib neurons, using both genetics and pharmacology. Simultaneous RNAi knockdown of IP_3R- and RyR-encoding genes selectively blocks acute PHP in phasic MN-Is neurons, with no effect in tonic MN-Ib neurons. The effect of targeting these channels may require developmental time because pharmacological blockade of IP_3R/RyR does not impair PHP in acute either subtype. Additionally, chronic PHP challenges like glutamate receptor subunit deletion reveal a broad role for both IP_3R and RyR - RNAi knockdown of these factors disrupts chronic PHP in both neuronal subtypes. In separate work, we addressed how synaptic ATP sources also contribute to this form of NMJ plasticity. Interestingly, phasic NMJ motor neurons appear to be metabolically fragile, failing to express acute PHP when simultaneously challenged with hexokinase blockade and glutamate receptor impairment. Collectively, our findings demonstrate neuron-type-specific and temporally restricted engagement of intracellular Ca^{2+} release and metabolic pathways during PHP. This highlights how homeostatic plasticity employs differential Ca^{2+} dependent and bioenergetic strategies at diverse NMJ synapses to maintain synaptic stability.

Disclosures: B. Mallik: None. **C. Frank:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.07/L1

Topic: B.05. Synaptic Plasticity

Title: Environmental Novelty Influences Arc-Associated Plasticity in the Entorhinal Cortex Under High-Fat Diet Conditions

Authors: *S. GONZÁLEZ TREJO[1], S. HERNÁNDEZ-RAMÍREZ[2], B. X. DÁVILA-PÉREZ[4], K. R. GUZMAN-RAMOS[3];
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Abstract: High-fat diet (HFD) consumption has been associated with alterations in neuronal plasticity and memory-related brain circuits. The entorhinal cortex is a critical component of the network supporting spatial information processing and hippocampal function. Activity-regulated cytoskeleton-associated protein (Arc) is an immediate early gene involved in activity-dependent synaptic plasticity and memory formation. Environmental novelty is a potent stimulus for neuronal activation and may influence plasticity-related molecular pathways under both physiological and metabolic challenge conditions. Mice were assigned to a 2x2 experimental design consisting of control or HFD feeding and standard housing or environmental novelty conditions. Metabolic status was evaluated using an intraperitoneal glucose tolerance test (IPGTT), and spatial learning and memory were assessed using the Morris Water Maze. Although all groups acquired the spatial task across training sessions, differences in memory-related performance measures were observed among experimental conditions, particularly in animals exposed to a high-fat diet without environmental novelty. Following behavioral testing, brains were processed for Arc immunohistochemistry, and Arc-positive cells were quantified in the entorhinal cortex. Differences in glucose tolerance and Morris Water Maze memory performance were observed among experimental groups. Arc expression within the entorhinal cortex also varied across experimental conditions. These findings suggest that metabolic and environmental factors may influence activity-dependent plasticity mechanisms in a brain region critically involved in spatial information processing. The present findings indicate that environmental novelty and dietary condition are associated with metabolic, behavioral, and molecular changes related to neuronal plasticity. These results contribute to understanding how environmental experiences interact with metabolic status to shape the neural substrates of plasticity and spatial memory.

Disclosures: S. González Trejo: None. **S. Hernández-Ramírez:** None. **B.X. Dávila-Pérez:** None. **K.R. Guzman-Ramos:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.08/L2

Topic: B.05. Synaptic Plasticity

Support: FDU Grant IDH2338002/001

Title: Spatial synaptic regularization stabilizes learning across biological and artificial neural networks

Authors: *H. ZHU[1], Y. CHEN[2], R. ZHANG[3];
[1]Fudan Univ., Shanghai, China; [2]Univ. of Sci. and Technol. of China, Hefei, China; [3]Inst. for Brain and Intelligence, FUDAN UNIVERSITY, Shanghai, China

Abstract: How synaptic weights change during learning remains a fundamental question in neuroscience. The Hebbian learning rule explains activity-dependent synaptic strengthening, and later Hebbian modifications such as Oja's rule constrain temporal weight dynamics, but whether synaptic learning is also shaped by spatial relationships among synapses remains unclear. Using volume electron-microscopy connectomics from human left temporal cortex, we found that adjacent dendritic spines exhibit morphological clustering, whereas synaptic weights exhibit center elevation-surround inhibition organization pattern. We formalized this topology as a spatially constrained Hebbian rule that captures the observed nonlinear limit on neighboring high-weight co-amplification around strong synapses. Translating this principle into Spatial Synaptic Regularization (SSR) for artificial networks reduced catastrophic forgetting and stabilized sequential model adaptation by preserving high-rank, low-overlap representations and reorganizing learned directions away from interfering states. These results establish spatial synaptic topology as an organizing dimension of learning that constrains synaptic weight change in cortex and can be repurposed in artificial networks as a strategy for stabilizing plasticity and mitigating the stability-plasticity dilemma.

Disclosures: H. Zhu: None. **Y. Chen:** None. **R. Zhang:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.09/L3

Topic: B.05. Synaptic Plasticity

Support: FDU Grant IDH2338002/001

Title: Connectome-scale chemical lateralization predicts asymmetric memory computation in the adult Drosophila mushroom body

Authors: *Y. CHEN[1], L. YUANYUAN[2], T. SHI[4], H. ZHU[5], J. ZENG[3], R. ZHANG[6];
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Abstract: The adult Drosophila mushroom body (MB) is a bilateral circuit for associative memory, yet whether its two hemispheres implement distinct transmitter logic and how such asymmetry affects computation remain unclear. Here, we combined whole-brain connectome analysis, a FlyWire-constrained simulation platform, and DPM functional imaging to examine whether chemical lateralization in the MB contributes to memory-related odor computation. Across well-sampled Kenyon cell subtypes, predicted serotonergic input was enriched in the right MB, whereas predicted glutamatergic input was predominantly left-biased, with the strongest asymmetry in the alpha-prime/beta-prime lobe, a compartment implicated in memory consolidation. Because transmitter lateralization cannot be directly manipulated within individual flies, we used connectome-constrained counterfactual simulations on real ALPN-to-KC odor input patterns to compare biologically aligned, symmetrized, mirror-reversed, and shuffled transmitter-gate configurations. The biologically aligned configuration expanded odor representation space and preserved structured coupling between transmitter bias and ALPN-KC input channels, whereas mirror-reversed and shuffled configurations reduced coding capacity. These advantages emerged selectively under demanding memory regimes, including interference, similar-odor discrimination, and delayed conflict, but were weak or absent under simple immediate-memory conditions. DPM calcium imaging further supported a right-biased functional readout, consistent with the nearly exclusive ipsilateral DPM-to-KC wiring observed in the connectome. Together, these results suggest that chemical lateralization is not merely an anatomical asymmetry, but a circuit-level feature that may contribute to hemisphere-specific memory computation in the adult fly MB.

Disclosures: Y. Chen: None. **L. Yuanyuan:** None. **T. Shi:** None. **H. Zhu:** None. **J. Zeng:** None. **R. Zhang:** None.

Poster

PSTR344: Homeostatic and Adaptive Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.10/L4

Topic: B.05. Synaptic Plasticity

Support: NINDS Grant 15NS118408

Title: A comprehensive neurophysiological analysis of psilocin at an identified synapse in Aplysia

Authors: *H. P. YARBROUGH, M. L. WAINWRIGHT, R. MOZZACHIODI;
Life Sci., Texas A&M University-Corpus Christi, Corpus Christi, TX

Abstract: Psilocin, the active metabolite of psilocybin and agonist of serotonin (5-HT) receptors, promotes dendritic spine growth and synaptogenesis in mammalian and invertebrate neurons (Ly et al. 2018). However, whether these psychoplastogenic structural changes translate into lasting, measurable alterations in synaptic strength and/or excitability at identified neurons has remained

unresolved. Using the pleural-pedal ganglion preparation in the invertebrate model *Aplysia*, a tractable system to study neuronal plasticity, we investigated the long-term (24 h) effects of psilocin at excitatory glutamatergic sensory-motor neuron (SN-MN) synapses. 5-HT is known to induce long-term synaptic facilitation and increased SN excitability at these synapses (Kandel 2001).Intracellular recordings were used to assess SN and MN excitability and SN-MN synaptic strength pre-treatment and 24-h post-washout. SN and MN excitability were measured as action potential count during depolarizing current pulses. Synaptic strength was measured as the amplitude of the excitatory postsynaptic potential (EPSP) evoked in MNs by SN stimulation. Preparations (n=10 per group for EPSP; n=12–17 per group for excitability) were randomly assigned to one of these treatments: psilocin (10 μM in 0.2% acetonitrile as vehicle, 2-h bath application), 5-HT (50 μM, 5×5-min pulses with 20-min inter-pulse intervals), or vehicle (2-h bath application). Data were expressed as percent change from baseline and analyzed using Kruskal-Wallis tests.Psilocin significantly increased EPSP amplitude at 24 h post-washout in a manner statistically equivalent to 5-HT and significantly elevated over vehicle (Student-Newman-Keuls *post-hoc* test). 5-HT treatment significantly increased SN excitability compared to vehicle (Dunn's *post-hoc* test); whereas psilocin did not. Neither psilocin nor 5-HT significantly altered MN excitability.These results indicate that psilocin produces lasting functional strengthening of an identified glutamatergic synapse without altering neuronal excitability. These findings are consistent with psilocin-induced structural remodeling reported in mammalian and invertebrate neurons (Ly et al. 2018), and support *Aplysia* as a tractable model for investigating the synaptic mechanisms of psychedelic compounds.

Disclosures: H.P. Yarbrough: None. **M.L. Wainwright:** None. **R. Mozzachiodi:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.01/L5

Topic: B.08. Epilepsy

Support: NINDS K00NS125773

Title: Identifying neuronal population-level activity changes in the development of viral infection-induced epilepsy

Authors: *L. BELL, E. H.-A. NIEH;
Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: Viral encephalitis is a growing global health burden affecting millions of people each year and remains a leading cause of acquired epilepsy. In temporal lobe epilepsy (TLE), seizures often originate within hippocampal circuits and progress through a stereotyped sequence of events: an initiating injury or infection, an acute period marked by inflammation and provoked seizures, and a latent phase during which circuit reorganization occurs before the onset of

chronic epileptic seizures. Importantly, early clinical intervention is often not feasible, highlighting the need to understand the processes that drive epileptogenesis during the post-infection window. Growing evidence suggests that epileptogenesis is likely driven by progressive alterations in network function that begin long before the onset of chronic spontaneous seizures. Though inflammatory responses, gliosis, and cellular remodeling are prominent features of this process, seizures ultimately arise from abnormal patterns of activity distributed across neuronal populations. Understanding how these population-level activity patterns emerge, stabilize, and interact together during the acute and latent phases of disease is critical for identifying new therapeutic and preventative strategies. Here, we utilize large-scale neuronal calcium imaging in the hippocampus of awake mice during acute seizures and latent periods of epileptogenesis. Using the Theiler's murine encephalomyelitis virus (TMEV) mouse model of infection-induced TLE, we identify longitudinal changes in the calcium activity of the hippocampal population. Initially, we find that the average calcium transient rate is significantly elevated across days of the acute seizure period, while the amplitude of calcium transients is significantly reduced. To understand whether this average change in calcium transients is a uniform shift across all neurons in the hippocampal population, we looked at the distribution of transient rates among individual neurons. Our data indicates that rather than a uniform shift in the rate of calcium transients, a small population of neurons with higher rates of calcium transients emerges by 5 days post-infection (dpi) and increases through 7dpi. These data suggest that infection drives a redistribution of activity within the hippocampal population and indicates that a subset of neurons may develop undue influence over network synchronicity and excitability. This analysis of population-levels changes thus begins to reveal how acute infection reshapes neuronal population activity, thereby encoding an increased susceptibility for seizure activity over time.

Disclosures: L. Bell: None. **E.H. Nieh:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.02/L6

Topic: B.08. Epilepsy

Support: Walter F. Heiligenberg Fellowship
NIH grant MH119179
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Title: Post-seizure changes in hippocampal neural network mechanisms and the coordinated recovery of hippocampal-dependent spatial working memory.

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Abstract: The hippocampus is required for working memory (WM) when the information to be held in mind is highly complex, novel, spatial, or is held over longer delays. Seizures in medial temporal lobe epilepsy often originate in the hippocampus and are found to impair WM. Many hippocampal neural-network mechanisms are altered post seizure including a disruption of theta oscillations, slow gamma oscillations, place field stability, as well as the rate and timing of neuronal firing patterns. However, it is not clear which mechanisms are critical for the recovery of WM post seizure, or whether partial restoration of select mechanisms are sufficient. To inform these questions we observed continuous changes in hippocampal neural network mechanisms in a hippocampal-dependent spatial WM task (8-arm radial maze), from intact WM pre seizure to the full recovery of WM post seizure. Ensembles of CA1 principal neurons (n = 263) were assessed from five pretrained male rats (WM performance >80% correct trials), with seizures induced acutely by stimulation to the ventral hippocampal commissural fibers following 4 baseline WM trials. Immediately following the electrographic acute hippocampal seizure brain oscillations were suppressed, CA1 neurons silenced and WM impaired. However, animals eventually resumed exploratory behavior, followed by reward seeking and then a return to performing the WM task, initially with substantial errors that improved steadily to baseline pre seizure performance levels (6.6 ± 3.1 trials until full WM recovery). Theta and slow gamma oscillations were the first to resume after seizure (1.0 ± 0.4 trials) albeit to lower theta frequencies (7.5 ± 0.3 Hz) than at baseline (8.3 ± 0.5 Hz), soon followed by a reemergence of CA1 firing rates. However, at this timepoint, WM performance had not recovered. Analyses of CA1 place fields revealed a major reorganization of the spatial representation of the maze with the seizure—many place cells turned off and new place cells turned on after seizure. Population activity further revealed the dismantling of the original spatial representation of the environment after acute seizure followed by the formation of a new map that required time to stabilize. The formation of the new spatial map was temporally aligned to the return of WM performance. However, theta phase precession remained impaired with the phase onset shifted to earlier phases. Taken together our data suggest that spatial WM does not require a full restoration of theta frequency, a retrieval of stored spatial maps, or precise temporal firing patterns, but can be supported once new stable spatial representations are re-established after seizure.

Disclosures: Y. Zhang: None. **Y. Feng:** None. **M. Wang:** None. **S. Leutgeb:** None. **J.K. Leutgeb:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.03/L7

Topic: B.08. Epilepsy

Support: NIH P01NS127769
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R35NS116852

Title: Extracellular chloride changes during post-traumatic epileptogenesis in living swine

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Abstract: There are currently no prophylactic treatments available to prevent post-traumatic epileptogenesis (PTE) and it is frequently medically intractable. The most common anatomical feature of PTE is astrogliosis; however, the link between gliosis and PTE remains unknown. TBI *is* linked to the release of matrix metalloproteinases and subsequent remodeling of the ECM. Preliminary data suggest that glia form ECM that is compositionally different from mature neuronal ECM. We hypothesize that this altered ECM has more densely sulfated proteoglycans, which "crowd out" chloride in the extracellular space (Cl_o). Here, we used *in vivo*, two-photon microscopy to image Cl_o, neuronal activity, and collagen throughout the latent period of epileptogenesis in a porcine model of post-traumatic epilepsy. Pigs were chosen because their gyrencephalic brains closely approximate human anatomy, grey:white matter ratio, and inflammation. We imaged before injury, immediately after bilateral cortical impact, and every two months following injury for >6months or until the animal developed spontaneous recurrent seizures. Extracellular chloride was measured using a novel dye (ABP-dextran); neuronal activity with genetically encoded calcium indicators (jRGECO1a or GCaMP8m); and fibrous collagen was assessed using its endogenous property of second harmonic generation (SHG). In a cohort of 10 injury sites in 8 pigs, cortical impact resulted in an acute increase in Cl_o, with a mean lifetime shift of 0.33ns (~25mM). In the first 4 pigs that completed the experimental protocol, two developed PTE, one was injured but did not become epileptic, and 1 was a sham. The two with PTE exhibited a decrease in Clo during the time window when behavioral seizures emerged. The pigs with PTE exhibited >20% *decrease* in Clo in the epoch during which they developed behavioral seizures, while the two pigs without PTE had <10% change in the same time window. Fibrous collagen was spatially heterogenous, but more frequently observed during later timepoints post-injury. Network analysis of calcium imaging data is ongoing, but preliminary functional connectivity analysis supports a small world network architecture. These preliminary findings are consistent with a model wherein TBI induces acute changes in the ECM that lead to secondary increases in extracellular chloride, a chronic increase in fibrous collagen, and chronic decrease in extracellular chloride at the site of injury during the time window when seizures emerged. Together these findings implicate disinhibitory changes to the extracellular matrix at the site of injury in post-traumatic epileptogenesis.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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Program #/Poster #: PSTR345.04/L8

Topic: B.08. Epilepsy

Support: Swebilius Foundation

Title: Long-term interictal connectivity changes in intracranial electrocorticography relate to therapeutic outcome in RNS patients

Authors: *T. YADAV[1], T. BUI[2], A. KUMAR[2], F. TU[4], T. GRAY[5], R. B. DUCKROW[6], L. HIRSCH[2], I. H. QURAISHI[3];
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Abstract: In the last two decades, responsive neurostimulation (RNS) has emerged as a key tool in achieving seizure control in patients with medically refractory focal epilepsy, yet response to therapeutic stimulation is highly variable. Previous work suggests that long-term intracranial stimulation suppresses seizures through gradual changes in the excitability of the network, which reduces the probability of transition from interictal to seizure. However, it is still unclear how interictal connectivity relates to outcome of therapy. To address this gap, we obtained electrocorticography (ECoG) data from 47 patients with RNS (25 females, 45.8 ± 13.4 years of age) and analyzed "scheduled" recordings within 2 years of implant. Patients were considered non-responders, intermediate responders, or super-responders if their disabling seizures at 2-year visit reduced by <50%, between 50-90% or >90% respectively relative to their pre-implant baseline. Inclusion criteria: patients implanted for >2 years, availability of seizure count at 2 years and availability of scheduled recordings. ECoG data was available from patients with mesial temporal (N=16) and neocortical (N=25) foci (4 channels per patient, 250 Hz sampling rate). Interictal connectivity was measured as phase-locking value (PLV, 0 to 1) of the background ECoG signal for within seizure foci and between seizure foci channels. Briefly this process involved removal of stimulation artifacts from ECoGs, estimation of phase using continuous wavelet transform (3-96 Hz) and computation of PLV as absolute mean phase difference between channels. Percent change in PLV was calculated relative to 90-day post-implant baseline (typical time before stimulation is enabled) and compared between non-responders and super-responders. For neocortical regions, within-foci connectivity was significantly higher in the alpha (8-15 Hz) band for super-responders ($p<0.05$, Wilcoxon ranksum test) while for mesial temporal region, this connectivity was significantly higher in the beta (15-30 Hz) and gamma (30-100 Hz) bands. Connectivity differences in different frequency bands may indicate an effect of therapeutic stimulation in network reorganization. While additional alternative measures of assessing changes in network connectivity are planned next, the interim findings suggest that therapeutic stimulation drives network reorganization and show the potential of using functional connectivity as a biomarker in guiding the choice of stimulation parameters for improved seizure control.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

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Topic: B.08. Epilepsy

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Title: Treatment-Induced Reorganization of Sleep Oscillatory Networks in Infantile Spasms: A Pilot Study

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Abstract: The developing brain's oscillatory networks during non-rapid eye movement (NREM) sleep reflect thalamocortical (TC) circuit integrity critical for neurodevelopment. In infantile epileptic spasms syndrome (IESS), disruption of these systems results in hypsarrhythmia. The impact of successful treatment on oscillatory dynamics remains underexplored. We investigated whether first-line treatment in IESS responders to corticosteroids reorganizes NREM sleep spectral architecture and cross-frequency coupling, reflecting recovery of physiological TC rhythms. Four infants (age 6-11 mo at diagnosis; 3 male) with IESS underwent overnight electroencephalography (EEG) at three time points: pre-treatment (Pre), early post-treatment (Post1), and consolidation post-treatment (Post2). All were confirmed responders to high-dose prednisolone. Thirty-second NREM epochs were analyzed for spike-wave index (SWI), spectral power across eight frequency bands (0.5-45 Hz; Welch's Method; FDR-corrected), and phase-amplitude coupling (PAC) quantified via modulation index across 11 frequency pairs encompassing delta, theta, alpha, and gamma bands. Linear mixed-effects models assessed longitudinal spectral changes. Successful treatment reduced SWI by 68.4% (7.95 ± 4.49% to 2.51 ± 0.99%; Cohen's d = 1.68, p=0.052), with three strong responders and one partial responder. Beyond seizure suppression, treatment reorganized the NREM spectral landscape: theta (118.3%, p_FDR = 0.005), alpha (76.3%, p_FDR = 0.007), sigma (111.6%, p_FDR = 0.021), and gamma power (138.5%, p_FDR = 0.033) increased significantly, while slow delta (−26.3%, p_FDR = 0.013) and delta power (−13.5%, p_FDR = 0.007) decreased. Notably, spike-wave band power was unchanged (p_FDR = 0.760) despite marked SWI reduction, suggesting reorganization of network topology rather than amplitude suppression. PAC analysis

demonstrated significant modulation of cross-frequency coupling across both spike wave discharges and NREM states ($p_{FDR} < 0.01$), consistent with restoration of hierarchical coupling. Successful first-line treatment of IESS may drive broad reorganization of NREM sleep oscillatory networks beyond just seizure suppression, restoring a spectral profile consistent with maturing TC dynamics. Sigma and gamma increases with delta suppression suggest partial recovery of TC inhibition. These findings provide insight into how anti-seizure treatment may recalibrate disrupted oscillatory hierarchies in the developing brain. Ongoing work aims to include additional patients, non-responders, and age-matched controls to separate treatment effects from developmental change.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.06/M2

Topic: B.08. Epilepsy

Title: Synergy between independent spike and high-frequency oscillation detectors for efficient clinical implementation

Authors: *A. C. SHINDHELM[1], W. C. STACEY[2], S. V. GLISKE[1];
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Abstract: Research objective and rationale Interictal electrographic features, including spikes and high-frequency oscillations (HFOs), are prominent biomarkers of epileptic tissue that provide additional information over just the seizure onset zone (SOZ). While existing research suggests that HFOs coincident with spikes have improved association with epileptic tissue in patients with drug-resistant epilepsy (DRE), most published papers focus on complex algorithms to assess this coincidence. Our objective was to assess whether simple temporal overlap between automated HFO and spike detectors was sufficient to show an improvement in the specificity of HFOs.
Methods Patients with DRE were selected from those undergoing intracranial EEG (iEEG) monitoring at the University of Michigan. Inclusion criteria included those who underwent resective surgery with over 80% of the SOZ resected and post-surgical freedom from disabling seizures (Engel Class I). This resulted in 11 subjects (13-55 years; 45.5% female). We computed interictal rates of spikes, HFOs, and coincident spike-HFOs for each electrode channel. Biomarker rates were evaluated in relation to the SOZ using asymmetry and area under the precision-recall curve (AUPRC). HFOs and spikes were detected using previously validated detectors. We evaluated whether coincident events had higher association with the SOZ than HFOs alone using paired one-sided Wilcoxon signed-rank tests ($\alpha = 0.05$).
Results In comparing biomarker performance in patients with DRE, coincident spike-HFOs had

higher association with the SOZ than HFOs alone, demonstrating that coincident spike-HFOs offer both higher precision (AUPRC *p*-value = 0.0015) and stronger concentration within the SOZ (median asymmetry = 0.74 versus 0.54, respectively; *p*-value = 0.0005).
Conclusions In addition to replicating that coincident spike-HFOs have higher association with the SOZ, our results demonstrate that independently running automated HFO and spike detectors is sufficient to find these co-occurring events. This reduces computational cost and increases the feasibility of translating these techniques into clinical practice.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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Program #/Poster #: PSTR345.07/M3

Topic: B.08. Epilepsy

Support: NINDA K99/R00 (1K99NS133494)

Title: Responsiveness and Awareness Testing in Epileptic Seizures (RATES): A standardized framework for evaluating consciousness in focal and generalized onset seizures

Authors: *A. SAXENA[1], A. KHALAF[1], A. YSMANOVA[1], M. GRUEN[1], H. MOSER FILHO[1], H. TUNG[1], A. PRAT[1], A. DE ALMEIDA CASTRO[1], H. YOSHIMURA[2,1], R. RIFKIN[1], N. SHAHANA[1], J. CONCEPCION[1], E. MAKINDE[1], J. VALDOVINOS RAMOS[1], B. ABDALLA[1], A. OSEI-BONSU[1], E. KLEINHENZ[1], S. YAN[1], L. HIRSCH[1], H. BLUMENFELD[1];
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Abstract: Accurate behavioral assessments are critical in evaluating consciousness in epileptic seizures; however, the frequency and adequacy of these assessments vary. As part of a larger study, we developed the Responsiveness and Awareness Testing in Epileptic Seizures (RATES) framework to grade and classify behavioral assessments during video-EEG monitoring. We retrospectively reviewed 601 seizures from 201 adults and classified behavioral assessments into responsiveness and awareness domains per ILAE definitions. Responsiveness was reviewed during the ictal period and graded on a four-tiered scale: Spared if all responses were normal, Mixed if normal and abnormal responses were present, Impaired if all responses were abnormal, and Unclear if responses were difficult to assess. Awareness was reviewed from seizure onset until 5 minutes after offset or video termination and separated into two report types: (1) phrase recall and (2) externally observable ictal events. Awareness assessments received grades using the same four-tiered scale as responsiveness. We considered a seizure assessed if it had responsiveness or awareness type 1 or 2 tested. Domain scores were used to assign each seizure an overall consciousness score depending on whether one or both domains were tested. If only

responsiveness or awareness was tested, overall grades matched the single tested domain. If both were tested, overall grades matched the higher domain score. This scoring paradigm was used since responsiveness and awareness can dissociate: patients may have normal responsiveness but no post-ictal recall, or conversely, patients may be unresponsive yet retain awareness of the ictal event. Both scenarios indicate preserved consciousness by ILAE criteria. Across 601 reviewed seizures, responsiveness was assessed in 571 (95.0%), awareness in 209 (34.8%), and both in 179 (29.8%). Of the 571 seizures with responsiveness tested, 155 had spared responsiveness (27.1%), 242 mixed (42.4%), 174 impaired (30.3%), and 1 unclear (0.02%). Of the 209 seizures with awareness tested, 135 had spared awareness (64.6%), 29 mixed (13.9%), and 45 impaired (21.5%). Of the 179 seizures with both tested, 109 were Spared (60.9%), 57 Mixed (31.8%), and 13 Impaired (7.3%). Across all seizures, overall consciousness scores were: 238 Spared (39.6%), 199 Mixed (33.1%), 164 Impaired (27.3%). Score distributions using the RATES framework highlighted substantial variability in behavioral testing. Responsiveness was tested far more frequently than awareness, despite both being important overall consciousness classification, underscoring the need for a more structured behavioral assessment approach.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.08/M4

Topic: B.08. Epilepsy

Support: NINDA K99/R00 (1K99NS133494)

Title: Event-Button Pressing as a Marker of Seizure Self-Awareness: Electroclinical Correlates in Scalp Video-EEG

Authors: A. YSMANOVA[1], A. KHALAF[2], A. SAXENA[3], M. GRUEN[4], E. MAKINDE[5], B. ABDALLA[4], *H. BLUMENFELD[3], H. MOSER FILHO[1], L. HIRSCH[1], R. RIFKIN[1], J. CONCEPCION[1], J. RAMOS[6], A. OSEI-BONSU[7], E. KLEINHENZ[1], N. SHAHANA[1], H. YOSHIMURA[8], A. PRAT[1], A. CASTRO[9], H. TUNG[10];
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Abstract: Patient-reported seizure counts are central to epilepsy management and research, but many events go unnoticed or unreported. We evaluated which seizure features predicted whether patients activated the bedside event button during inpatient long-term scalp video-EEG monitoring. In this retrospective cohort, we analyzed 601 seizures recorded in 201 adults (≥18 years) at a tertiary epilepsy center. Seizures were categorized by onset type (generalized vs focal), localization (temporal vs extratemporal), lateralization (right vs left), and consciousness state (preserved vs impaired responsiveness and awareness). For each seizure, we documented event-button activation (yes/no) and compared groups using chi-square tests. Overall, 91/201 patients (45.3%) pressed the button at least once. Only 227/601 seizures (37.8%) were accompanied by a button press, most occurring during the seizure (205/227, 90.3%) rather than after it ended (22/227, 9.7%). Button activation was substantially more common in generalized-onset than focal-onset seizures (28/33, 84.8% vs 191/504, 37.9%; $p < 0.001$), in temporal than extratemporal seizures (105/239, 43.9% vs 23/106, 21.7%; $p < 0.001$), and when consciousness was preserved versus impaired (152/238, 63.9% vs 17/164, 11.0%; $p < 0.001$). In contrast, press rates were similar for right- versus left-lateralized seizures (58/155, 37.4% vs 38/131, 29.0%; $p = 0.133$). Thus, fewer than 4 of 10 recorded seizures were self-reported via button pressing, typically during the ictal period. Reporting behavior was strongly associated with onset type, localization, and especially consciousness, underscoring that impaired consciousness markedly limits patient-initiated seizure reporting. These results emphasize constraints of patient-reported seizure counts and motivate further studies of additional electroclinical predictors of seizure awareness to inform clinical care and research design.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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Topic: B.08. Epilepsy

Support: NSERC Grant RT690332
Vanier Doctoral Scholarship
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Title: High-Resolution Multi-Region Recordings from Custom 3D Microelectrode Arrays Reveal the Circuit-Wide Functional Impact of Cannabidiol on Neonatal Rodent Hippocampal Seizure-Like Activity in vitro

Authors: *F. IQBAL[1], K. HAIDER[2], K. SHUKOOR[3], A. JOSHI[2], U. ZAIDI[2], D. FINCH[2], C. DALTON[2], K. YUSUF[2], N. I. SYED[4];

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Abstract: Epilepsy affects over 50 million people worldwide. Of these, neonates who experience severe seizures bear the highest rates of pharmacoresistance and neurodevelopmental risk. Current anti-seizure medications (ASMs) for this subpopulation may also exert lasting side-effects on key hippocampal learning and memory pathways. There is therefore a critical need for safer ASMs that can modulate severe seizure-like activity (SLA) in neonatal brain tissue. Alongside this, a better understanding of how these ASMs interact with key developmental pathways, such as cholinergic circuits, is required.

Cannabidiol (CBD) is an ASM of interest that was recently approved for adjuvant treatment of severe pediatric drug-resistant epilepsies. Expanded use trials have shown promise across several seizure syndromes; however, the direct functional impact on neonatal hippocampal circuitry has not been fully characterized. This precludes further comparative and mechanistic studies. A key barrier to this is the absence of low-cost tools capable of high-resolution, multi-region interrogation of activity across neonatal brain slices.

To address both challenges, we developed custom 3D microelectrode arrays (MEAs) using printed circuit board processes (~$20/chip), leveraging reproducible solid metal microneedle fabrication and polymer encapsulation to create a biocompatible platform for neonatal slice electrophysiology. Hippocampal slices from neonatal Sprague-Dawley rats at postnatal days 6-10 ($n \geq 5$ biological replicates per condition) were perfused with Mg^{2+}-free artificial cerebrospinal fluid to induce SLA. 1 μM CBD was administered and network excitability, burst dynamics, and spatial propagation across the trisynaptic circuit were quantified. We found that CBD acutely modulated CA3 activity during ongoing Mg^{2+}-free SLA, which is a key region for regulating network hyperexcitability.

Having established these effects, we next interrogated how pharmacological blockage of nAChRs, which modulate neonatal hippocampal excitability, modifies CBD-mediated attenuation of SLA in early-age hippocampal circuits. To our knowledge, this work provides the first multi-region characterization of the functional impact of CBD on neonatal hippocampal SLA using such a platform, and identifies receptor-specific pathway contributions that are critical for evaluating the efficacy of this drug during a critical neurodevelopmental window. These findings lay the groundwork for systematic, mechanism-informed ASM screening in neonatal circuits, and contribute to the knowledge base needed to advance safer treatment options for this underserved population.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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National Institutes of Health Grant R21NS131903

Title: Improving Noninvasive Seizure Screening in Preclinical Rodent Epilepsy Models Using Dynamical Machine Learning Approaches

Authors: *M. LAVIN[1], D. HUFFMAN[3], M. SUMITHRARACHCHI[2], B. BAUER[2], S. SUNDERAM[1];
[1]F. Joseph Halcomb III, M.D. Dept. of Biomed. Engin., [2]Dept. of Pharmaceut. Sci., Univ. of Kentucky, Lexington, KY; [3]Signal Solutions, LLC USA, Lexington, KY

Abstract: Viable noninvasive approaches to seizure screening would greatly benefit preclinical research using rodent epilepsy models. However, it is difficult to distinguish seizure-related movements from other behaviors using motion or video-based measurements. This leads to high rates of false positive detections and more time spent reviewing and rejecting them. To overcome this limitation, we examined how modeling seizure dynamics in piezoelectric ("piezo") motion signals (Signal Solutions, LLC) using machine learning algorithms impacted seizure detection accuracy. We recorded four weeks of piezo data in Wistar rats (n=32) treated with pilocarpine, extracting 30-second chunks from the 40 most intense events per animal per week based on the peak values of a moving line length ratio (LLR) metric. Each event was labeled as either seizure (n = 843) or non-seizure (n = 3999) behavior based on video review. We then extracted 10 piezo signal features in 0.5-second windows and combined them into a single Fisher discriminant feature (FDF) that maximizes the ratio of between-class to within-class differences. The FDF time sequences for labeled events were then used to train five machine learning algorithms: a simple FDF threshold; two linear discriminant analysis (LDA) models, one based on the statistical moments of the distribution of FDF values (non-dynamical) and the other on the moments of the sequence or "shape" of FDF values (dynamical); an artificial neural network (ANN); and a long-short-term memory network (LSTM). We included an LLR threshold method as a reference. In an eightfold cross-validation, the two threshold methods produced similar sensitivities, reaching around 80%, with the FDF threshold showing higher specificity (75.8±0.9% vs. 38.1±3 %) and precision (41.0±0.6% vs. 22.6±0.6%). Of the LDA models, the statistical moment model outperformed its dynamic shape moment counterpart across all metrics, achieving a specificity of 88.1±0.4%, a precision of 56.6±1%, and a sensitivity of 73.3±1 %. Among the neural networks, the LSTM slightly outperformed the ANN, with a specificity of 87.9±2%, a precision of 59.4±4%, and a sensitivity of 75.2±1 %. We applied these models to a completely out-of-sample recording of one week of data from 16 Wistar rats. The results were consistent with the cross-validation, with the LSTM producing a sensitivity of 77.3% and specificity of 86.4%, and the sample-moment LDA producing a sensitivity of 73.5% and specificity of 86.9%; both reached a precision of about 55%. Preliminary testing on a small sample in a mouse model of epilepsy showed similar results, and we are in the process of expanding the sample to allow a more thorough analysis.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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AES Junior Investigator Award
NIH RF1AG072497
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NIH R21 DA0495658

Title: Progression of medial entorhinal spatial coding deficits in a mouse model of temporal lobe epilepsy

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Abstract: BACKGROUND: Temporal lobe epilepsy (TLE) is a debilitating disorder that includes pervasive memory impairments that significantly impact patient quality of life. Using rodent models of TLE, our lab has previously shown progression of learning and memory impairments along with spatial coding deficits in the hippocampus. Whether these impairments in hippocampal spatial coding are due to only local processing deficits or can be attributed to altered spatial coding in upstream regions remains poorly understood. Indeed, hippocampal inputs from the medial entorhinal cortex (MEC) have been shown to be spatially modulated and their activity is necessary to facilitate hippocampal spatial memory and encoding. Furthermore, seizures have been shown to cause transient reorganization of MEC circuits due to cell damage.
METHODS: We used viral vector constructs for layer specific calcium indicator expression in either MECII stellate cells or MECIII excitatory neurons and performed in vivo calcium imaging with Miniscopes in freely behaving mice as they performed a battery of spatial foraging or memory tasks.
RESULTS: Our data suggests that pilocarpine induced TLE causes disruptions to the spatial coding of both MECII stellate cells and MECIII neurons. In particular, we have found reduced stability of spatial representations in MEC of epileptic mice, which emerged earliest in MECIII

neurons. In addition, we have found that TLE dysregulates grid populations in MEC. Specifically, epileptic mice have fewer grid cells out of both MECII stellate cell and MECIII neuron total populations. Preliminary data suggests that those remaining grid cells have altered grid architecture such as smaller grid spacing. Thus, this region appears to be a potential site of early dysfunction in epilepsy.
CONCLUSIONS: These preliminary results suggest that CA1 spatial coding deficits may be due in part to altered inputs and implicates upstream MEC as another site of functional pathology in TLE. Together, this work uses state-of-the-art recording techniques to determine precisely where and how spatial coding breaks down in epileptic mice, revealing new insights into the cause of cognitive deficits.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

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Title: Medial entorhinal layer 2 stellate cell activity is sufficient to drive type 2 dentate spikes and pathological hypersynchronous events in healthy and epileptic mice

Authors: *P. A. PHILIPSBERG[1], E. M. COLEMAN[1], Z. CHRISTENSON WICK[1], Y. FENG[1], K. M. PIMSHAN[1], C. KOHLER[1], C. G. KENTROS[2], T. SHUMAN[1];
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Abstract: In healthy brains, synchrony between brain regions is thought to support memory, while in epileptic brains, pathological hypersynchrony is thought to disrupt memory. Here we investigate the mechanisms giving rise to type 2 dentate spikes (DS2s), a synchronous event in dentate gyrus thought to be important for memory consolidation and behavioral state-switching. Despite a growing body of literature indicating the importance of DS2s in behavior, relatively

little is known regarding how these events are generated. Medial perforant path projections have long been thought to drive DS2s, however the specific contribution of medial entorhinal layer 2 (MEC2) stellate cells to DS2s has never been experimentally tested. Similarly, the mechanisms that give rise to interictal epileptiform discharges in the epileptic hippocampus remain largely unknown. Here we investigate the contribution of MEC2 stellate cells to both DS2s and IEDs. We performed dual region silicon probe recordings in MEC and CA1/DG of both healthy and chronically epileptic pilocarpine-induced status-epilepticus mice. We expressed ChR2 in medial entorhinal layer 2 stellate cells in order to identify and track the activity of these specific cells surrounding DS2s and IEDs. We found that the firing rates of MEC2 stellate cells increase preceding a DS2 and that this modulation of firing rate is increased in epileptic mice, which also have higher rates of DS2s. Finally, we found the over activating stellate cells with high intensity optogenetic stimulation was sufficient to drive IED-like events in both epileptic and healthy control mice. These results provide new evidence that MEC2 stellate cell activity contributes both to physiological DS2s and is sufficient to induce pathological hypersynchronous events in epilepsy. This provides a novel therapeutic target for treating hypersynchrony contributing to seizures and cognitive impairments in temporal lobe epilepsy.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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CURE Taking Flight Award
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American Epilepsy Society Postdoctoral Fellowship

Title: Interneuron theta phase locking controls seizure susceptibility

Authors: *Z. CHRISTENSON WICK, P. A. PHILIPSBERG, C. KOHLER, S. I. LAMSIFER, E. KATANOV, K. GORDON, Y. FENG, L. M. VETERE, C. D. ADAM, G. DONNELLY, D. J. CAI, T. SHUMAN;
Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Network-wide oscillations, such as theta, orchestrate and organize the spiking of individual neurons. This leads many neurons, particularly interneurons, to be active at specific

phases of oscillations, a phenomenon known as phase locking. This precise temporal organization of spiking is thought to be critically important for maintaining excitatory-inhibitory homeostasis and network function, though the causal influence of this phenomenon has never been determined. Here, we've found altered theta phase locking of PV+ interneurons in the dentate gyrus of epileptic mice and directly test the hypothesis that inhibitory theta phase locking can bidirectionally control seizure susceptibility. To test this hypothesis, we developed a low-latency closed-loop optogenetic system (PhaSER) to bidirectionally control inhibitory phase locking to theta in head-fixed control and pilocarpine-treated epileptic mice. We then applied our closed-loop system to directly control the phase locking of these dentate interneurons to their preferred or non-preferred phase of theta while measuring latency to seize after a systemic kainic acid injection. In control mice, both PV+ and SOM+ interneurons in the dentate gyrus are primarily active at the trough of CA1 theta oscillations, while in epileptic mice PV+ cells have disrupted phase locking. We found that mis-aligning PV+ cell spiking to the peak of theta increased seizure susceptibility in otherwise healthy, control mice and that re-aligning PV+ spiking to the trough of theta diminished seizure susceptibility in epileptic mice with phase locking deficits. On the other hand, manipulating SOM+ cell phase locking did not impact seizure susceptibility in either control or epileptic animals. We also found a stark sex difference, with epileptic males showing more severe phase locking deficits than epileptic females and, consistent with this sex difference, we found that re-aligning PV+ cell phase locking in epileptic males was effective at reducing seizure susceptibility while the same therapeutic effect was not found in epileptic females. These data suggest that theta phase locking of PV+ cell spiking plays an important and causal role in seizure susceptibility. These data also suggest that the mechanisms of seizure susceptibility may be different in male and female pilocarpine-treated mice. Gaining deeper insights into the impacts of inhibitory theta phase locking will reveal the potential of oscillation-driven stimulation as an effective epilepsy therapeutic, and the direct influence that specific interneurons' theta phase locking holds over network-wide activity.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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Topic: B.08. Epilepsy

Support: 1F32NS146143 - NINDS
1R01NS136590 - NINDS

Title: Circuit editing to boost long-range feedforward inhibition decreases chronic seizures in experimental temporal lobe epilepsy

Authors: *C. D. ADAM[1], K. TOOLE[2], A. SAXENA[1], C. GARCIA JOU[1], K. DZIRASA[3], T. SHUMAN[4];
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Abstract: Temporal lobe epilepsy (TLE) is a debilitating disorder characterized by spontaneous, reoccurring seizures and pervasive learning and memory deficits. The hippocampal dentate gyrus (DG) is implicated in seizure generation and supports cognitive processes that are disrupted in TLE. Importantly, stereotyped patterns of cell loss and circuit reorganization within the DG have been reported in animal models and clinical cases of TLE. Preliminary work from the lab has specifically demonstrated a loss of long-range medial entorhinal cortex (MEC) input to parvalbumin positive (PV+) interneurons in the DG. We hypothesized that increasing the connectivity strength of remaining MEC inputs specifically onto DG PV+ interneurons would boost feedforward inhibition and decrease chronic seizure burden. To test this hypothesis, we utilized the recently developed Long-term integration of Circuits using connexins (LinCx) system which was designed to manipulate the strength of connectivity between specific neuronal subpopulations using the virally expressed engineered gap junctions Cx34.7M1 and Cx35M1. LinCx constructs exclusively link to each other forming heterotypic, rectifying gap junctions that preferentially pass current in the Cx34.7M1 to Cx35M1 direction, boosting the strength of connectivity between synaptically connected cells in a unidirectional manner. In order to test our hypothesis, PV-cre mice were injected with pilocarpine to induce chronic epilepsy, then implanted with an EEG electrode for continuous seizure monitoring. After a baseline recording period of at least 3 weeks, mice received viral injections of functional LinCx constructs (Cx34.7M1 in MEC excitatory cells and Cx35M1 in DG PV+ interneurons) or non-functional controls (GFP in MEC excitatory cells and Cx35M1 in DG PV^{+} interneurons). Continuous EEG monitoring was resumed 6 weeks after viral injections, and seizures were identified and compared across groups. Mice that received LinCx showed a significant reduction in seizure frequency as measured by the number of seizures per day. When compared to baseline, seizure rates decreased by ~40% in LinCx animals while they more than doubled in controls. Overall, we found that increasing connectivity between excitatory cells in MEC and DG PV+ interneurons not only stops seizures from worsening over time, but actually decreases seizure frequency in mice. This suggests that feedforward inhibition from MEC to DG PV+ interneurons is a critical mediator of seizure susceptibility and boosting this connection is a viable therapeutic strategy to reduce seizures.

Disclosures: C.D. Adam: None. **K. Toole:** None. **A. Saxena:** None. **C. Garcia Jou:** None. **K. Dzirasa:** None. **T. Shuman:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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Program #/Poster #: PSTR345.15/N7

Topic: B.08. Epilepsy

Support: R01NS136590
F32NS146143

Title: Disrupted Long-Range Inputs to Dentate PV^+ Interneurons in Experimental Temporal Lobe Epilepsy

Authors: *K. A. TOOLE[1], A. SAXENA[2], C. D. ADAM[3], T. SHUMAN[4];
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Abstract: BACKGROUND: Temporal lobe epilepsy (TLE) is a neurological disorder characterized by recurrent seizures and is often comorbid with cognitive deficits, including impairments in learning and memory. The hippocampal dentate gyrus (DG) plays a critical role in these processes and is known to be disrupted in both TLE patients and animal models. Parvalbumin-positive (PV^+) interneurons provide fast, feedforward inhibition that is essential for limiting overexcitation in the DG. Previous work from ourlab demonstrates that the spike timing of DG PV^+ interneurons is disrupted in TLE, impairing their normal function. However, it remains unclear whether dysfunction in these PV^+ interneurons arises from alterations in their upstream synaptic inputs.
METHODS: To test this, we administered a cre-dependent modified monosynaptic retrograde rabies virus to PV-Cre mice. TLE was induced using pilocarpine, and tracing experiments were conducted approximately 22 weeks post-induction. A cre-dependent helper virus was first injected into the DG to restrict rabies infection to PV^+ interneurons and enable single-synapse retrograde spread. This approach allowed us to map and quantify presynaptic inputs to DG PV^+ cells in control and epileptic mice.
RESULTS: Compared to controls, epileptic mice showed an overall reduction in long-range presynaptic input cells with a statistically significant loss of input from the medial entorhinal cortex (MEC). No differences were observed in the number of starter cells.
CONCLUSIONS: Our findings indicate that long-range cortical inputs, particularly from the MEC, onto DG PV^+ interneurons are selectively disrupted in chronic TLE. This loss of upstream drive may contribute to impaired feedforward inhibition and dentate gyrus dysfunction. Targeting these circuits may provide new therapeutic strategies for TLE.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

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Program #/Poster #: PSTR345.16/N8

Topic: B.08. Epilepsy

Support: R01 NS126594-01

Title: Closed-loop optogenetic modulation of corticothalamic circuits in a mouse model of absence epilepsy

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Abstract: Generalized seizures are epileptic events that involve both hemispheres of the brain from onset, leading to widespread disturbances in neural activity. Absence seizures, a specific type of generalized seizure primarily affecting children aged 4 to 14, are characterized by brief interruptions in consciousness accompanied by synchronized 3 Hz spike-wave discharges (SWDs) in the electroencephalogram (EEG). With advances in epilepsy treatment, responsive neurostimulation (RNS) has emerged as a closed-loop system that monitors brain activity and delivers electrical stimulation (ES) only when abnormal patterns are detected, thereby increasing precision and reducing unnecessary stimulation. However, the exact structures contributing to seizure control remain unclear because ES can spread across extensive brain regions. Therefore, this study utilized C3H/HeJ mice with spontaneous absence seizures. By integrating electrocorticography (ECoG) recording with closed-loop optogenetic inhibition, we aimed to identify structures within the corticothalamic circuit that maintain or terminate absence seizures. The somatosensory cortex and five thalamic nuclei were tested individually, including the thalamic reticular nucleus (RT), the ventrobasal thalamus (VB), the posteromedial thalamic nucleus (POm), the centromedian thalamic nucleus (CM), and the parafascicular nucleus (PF) of the thalamus. We employed a voltage-amplitude-based seizure detection algorithm with an approximately 3 ms delay between spike detection and light stimulation. Among the tested regions, optogenetic inhibition of RT produced the fastest seizure termination, aborting SWDs within 0.5 s. In contrast, inhibition of other structures, including POm and VB, had limited effects on seizure maintenance. These findings suggest that RT is a critical node for controlling ongoing absence seizures and may represent a promising target for circuit-specific closed-loop intervention. More broadly, this work helps define corticothalamic mechanisms that sustain absence seizures and may guide future therapeutic strategies for childhood absence epilepsy.

Disclosures: S. He: None. **Y. Zhang:** None. **M.P. Beenhakker:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

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Program #/Poster #: PSTR345.17/O1

Topic: B.08. Epilepsy

Title: Mouse behavioral seizures and the use of machine learning models for their detection and analysis

Authors: *H. KIM[1], H. SEO[1], R. LEE[2], S.-H. LEE[2], S. KIM[2];
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Abstract: Epilepsy is a serious and often lifelong neurological disorder affecting more than 50 million people worldwide, with approximately one-third of patients remaining refractory to currently available antiseizure medications. Accurate seizure detection and monitoring are essential for both clinical management and preclinical therapeutic development; however, existing approaches have important limitations. Although electroencephalography (EEG) remains the clinical gold standard for seizure detection, its application in animal studies is constrained by challenges such as minimal or ambiguous electrographic changes, electroclinical dissociation, and the inability to fully capture behavioral manifestations of seizures. To address these limitations, we developed a tri-axial behavioral monitoring platform consisting of one overhead and two lateral cameras that provide unobstructed, high-resolution visualization of mouse behavior, including fine appendicular and orofacial movements. To generate a robust seizure-enriched dataset, mice received intraperitoneal kainic acid (KA), and KA-induced seizures were recorded and manually scored using the modified Racine scale. These human-annotated recordings served as training data for seizure intensity classification. We subsequently developed an end-to-end spatiotemporal deep learning framework based on a Convolutional Neural Network-Long Short-Term Memory (CNN-LSTM) architecture to automatically identify seizure-related behaviors from multi-view video recordings. We demonstrate the feasibility of a multi-view behavioral machine learning approach for automated seizure detection. Collectively, this work establishes a foundation for more sensitive and objective seizure monitoring in preclinical epilepsy research.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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Program #/Poster #: PSTR345.18/O2

Topic: B.08. Epilepsy

Support: NIH Grant R01 NS097762-06
NIH Grant F30 NS145620-01

Title: The Role of Frontal Corticothalamic Circuits in Epilepsy

Authors: *A. SUKHAREV[1,2], S. VICINI[3], P. A. FORCELLI[3];
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Abstract: Epilepsy affects approximately three million U.S. adults with one-third of patients displaying inadequate seizure control with drug therapy alone. Deep brain stimulation for drug-resistant epilepsy is a promising therapy, but current targets leave many patients with incomplete seizure control. Previous studies from our group have shown that inhibition of the mediodorsal nucleus of the thalamus (MD) and its projections to the prelimbic cortex (PrL)—the rodent

homolog of the human dorsal anterior cingulate cortex—suppresses focal onset seizures in the amygdala-kindling model of temporal lobe epilepsy in rats. However, it is unknown how recurrent seizures may change the function of the PrL, and directly targeting the PrL has not been examined for seizure control. To address this gap, we used amygdala-kindling in Sprague Dawley rats, combined with chemogenetic modulation of PrL and slice electrophysiology. Rats were injected with a mix of AAV encoding channelrhodopsin and retrobeads to allow for labeling of PrL corticothalamic (CT) cells that project to the MD and simultaneous activation of MD terminals in the PrL. A second group was injected with an inhibitory Designer Receptor Exclusively Activated by Designer Drugs (DREADD) construct in the PrL to test the effect of focal PrL silencing on amygdala-kindled seizures. After surgery, rats were stimulated daily until displaying 5 generalized clonic seizures. For recordings, rats were perfused and coronal sections containing the PrL were cut. For chemogenetic testing, rats were tested while blinded to treatment at the minimum seizure threshold after receiving intraperitoneal 0.5 mg/kg Deschloroclozapine or an equivalent volume of vehicle. DREADD-expressing rats were also retested with 5 mg/kg Clozapine-N-Oxide or vehicle to test the efficacy of different DREADD agonists. In kindled rats, layer 5 CT cells (n=23 cells, N=8 rats) in the PrL show depolarized resting membrane potential and increased firing rate as compared to sham rats (n=12 cells, N=5 rats) Layer 5 CT cells in the PrL of kindled rats (n=4 cells, N=1 rat) displayed reduced amplitudes of optogenetically-evoked thalamic input compared to sham (n=4 cells, N=2 rats), as well as reduced amplitude of spontaneous excitatory input. In parallel, kindled rats displayed a striking increase in the frequency of spontaneous excitatory input. When DREADD-expressing kindled rats (n=8 rats) were treated with DCZ or CNO to activate the inhibitory DREADD, amygdala-kindled seizures were completely suppressed. Together, these data indicate that repeated seizures alter the excitability of the PrL and that silencing the PrL is an effective strategy to reduce seizures.

Disclosures: A. Sukharev: None. **S. Vicini:** None. **P.A. Forcelli:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.19/O3

Topic: B.08. Epilepsy

Title: Low-mortality chronic epilepsy model using fractionated kainic acid dosing and seizure imaging with functional ultrasound

Authors: R. IMMONEN, T. BRAGGE, **J. RYTKÖNEN**, A.-M. PENTTINEN, *T. HUHTALA;
IQVIA Labs. Finland Oy, Kuopio, Finland

Abstract: Chemically induced chronic epilepsy models mimic temporal lobe epilepsy (TLE) and are typically utilized in anticonvulsant drug research. The models are induced either by inducing

an initial episode of prolonged continuous seizure (Status epilepticus) with a large dose of chemoconvulsant e.g. kainic acid (KA) or by repeated sub-convulsive stimulations (chemical kindling). The former induction method is faster than the latter but typically causes mortality already in the early phase before the TLE model has fully developed. This does not support 3Rs of test-animal usage. In this study we used fractionated KA dosing to reach status epilepticus to reduce the mortality of the model.
Two parallel cohorts of adult C57BL/6J male mice were studied. In the first cohort, a model of chronic epileptic activity was established by induction of status epilepticus with fractionated KA injections (10 mg/kg + 10 mg/kg + 5 mg/kg + 5 mg/kg, 30-min interval, i.p, total dose 30 mg/kg). The development of epileptic activity was confirmed by continuous 3-weeks EEG recording (cortical electrodes over the hippocampus). In the second cohort, epilepsy was induced by fractionated KA injections as established in the first cohort and functional ultrasound (fUS) imaging utilizing slow KA infusion challenge was performed in the chronic epileptic animals 4 weeks after the model induction. The fUS imaging was used to characterize the activation pattern induced by slow KA infusion under ketamine-medetomidine anesthesia (KA i.p. 10 mg/kg, 10 mL/kg over 30 min infusion). The 55-min fUS scan consisted of a 5-min baseline, and a 50-min follow-up of the response in relative cerebral blood volume (rCBV) during and after the 30-min infusion.
Induction of chronic epileptic activity with fractionated KA injections in mice was successful with 0% acute mortality, and spontaneous epileptiform activity, spiking and seizures manifesting in all animals. In chronic epileptic animals, fUS imaging was used to visualize hippocampal activation and spreading to the cortex and thalamus indicating epileptiform activation and seizure generalization during a slow infusion of KA challenge. Fractionated KA dosing reduces mortality in the induction of status epilepticus. Furthermore, the fUS platform with sub-seizure KA challenge allows testing of novel seizure threshold modulating treatments.

Disclosures: R. Immonen: A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **T. Bragge:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **J. Rytkönen:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **A. Penttinen:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **T. Huhtala:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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Topic: B.08. Epilepsy

Support: NYS Institute for Basic Research Fellowship in Developmental Neuroscience and Developmental Disabilities (to HJR)
Research Foundation of SUNY (to DSFL)

Title: Identification of Physiological Biomarkers for Post-Traumatic Epilepsy After Severe Cortical Injury in Rats

Authors: *H. J. RICE[1], A. MEJIA-BAUTISTA[1], D. S. LING[2];
[2]Physiol. and Pharmacol., [1]SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY

Abstract: Post-traumatic epilepsy (PTE) is a chronic, difficult to treat epilepsy subtype that develops after a traumatic brain injury (TBI). Despite decades of research, clinicians cannot reliably predict which patients will develop PTE. This study looks to address this critical unmet need by uncovering robust, predictive physiological biomarkers of PTE. We conducted epidural electroencephalography (EEG) recordings in a rodent model of TBI. This model uses the controlled cortical impact (CCI) procedure to induce a severe cortical injury, which leads to epileptiform activity and seizures in up to 40% of rats. Video-EEG (vEEG) was recorded over 24-hour periods in the acute (days 0-14) and chronic (days 15-200) phases. Acute recordings are designed to detect early biomarkers including electrical and sleep patterns. Chronic recordings are evaluated for spontaneous recurrent seizures (SRSs) to determine PTE status. This preclinical pipeline also explores the efficacy of acute therapeutic interventions including early administration of brivaracetam (BRV), a synaptic vesicle glycoprotein 2A ligand anti-seizure medication. Here we present data from over 8,500 hours of recordings across 21 Sprague Dawley rats (10 CCI, 7 Sham, 4 CCI-BRV). Severe CCI injury leads to chronic spontaneous seizure activity in rats that can be detected via wireless vEEG monitoring within 6 weeks after injury. EEG data demonstrates robust recordings up to 8 months post-implantation and displays oscillatory elements consistent with behavioral states. Semi-autonomous detection pipelines were integrated to detect seizures and behavioral states. Shifts in neural oscillations in CCI animals were detected in spectrograms that could serve as potential predictive biomarkers for PTE.

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Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

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Topic: B.08. Epilepsy

Support: NIH R01NS120945

Title: Modulation of Basal Ganglia Dopamine Signaling Alters Frontal Lobe Seizures

Authors: *B. ALMAGUER[1], J. KAPUR[2];
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Abstract: The basal ganglia organizes motor behavior, and it's predominantly controlled by two major neural pathways: the direct and indirect pathway. The direct pathway comprises of

dopamine receptor D1 (DRD1)-expressing medium spiny neurons (MSNs) that project to the globus pallidus internus and substantia nigra pars reticulata (SNPr) to facilitate voluntary movement. The indirect pathway inhibits voluntary movement via dopamine receptors D2 (DRD2) on MSNs projecting to the globus pallidus externus, subthalamic nucleus, and SNPr. We have previously demonstrated that frontal lobe seizures preferentially activate DRD2 MSNs of the indirect pathway. Whether direct or indirect neural pathways of the basal ganglia differentially regulate frontal lobe seizure activity remains unclear. We hypothesize that activation of the indirect pathway suppresses seizures, whereas activation of the direct pathway exacerbates them. We used 6-8week-old male and female C57BL/6 mice. Frontal lobe seizures were induced by stereotactic implantation of 1.7 mg cobalt wire into the frontal cortex. During the same surgery, mice were also implanted with a bilateral striatal cannula, cortical EEG electrodes, and a cerebellar reference electrode. Following recovery, continuous video-EEG monitoring was performed. Fourteen hours after cobalt implantation, mice received bilateral intrastriatal infusions (1 µl/hemisphere) of the DRD1 agonist SKF 81297 hydrobromide (1 µg/µl), DRD2 agonist sumanirole maleate (10 µg/µl), or DRD1 antagonist SCH 23390 hydrochloride (5 µg/µl) to selectively modulate seizures propagating through the direct and indirect neural pathways of the basal ganglia. Activation of the direct pathway with a DRD1 agonist increased seizure frequency and was associated with progression to status epilepticus and mortality. In contrast, activation of the indirect pathway with DRD2 agonist decreased seizure frequency. Similarly, DRD1 antagonist was associated with a reduction in seizure frequency. Further quantitative analysis of video-EEG recording is ongoing. These preliminary findings suggest that activation of the indirect pathway suppress frontal lobe seizure activity, whereas activation of the direct pathway promotes seizures. Together, these results support a modulatory role for basal ganglia circuity in seizure control and identify dopamine-receptor-dependent pathways as potential therapeutic targets for frontal lobe epilepsy.

Disclosures: B. Almaguer: None. **J. Kapur:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.22/O6

Topic: B.08. Epilepsy

Support: NIH R01 NS066974

Title: Disruption of Cortical Arousal Neuromodulation in Focal and Focal to Bilateral Tonic-Clonic Seizures with Impaired Consciousness

Authors: *J. LIU[1], V. DOAN[1], Y. ZHENG[1], S. CHOPRA[1], L.-M. FINGER[1], J. ABRAHAM[1], H. WEN[1], J. A. CARDIN[2], H. BLUMENFELD[3];
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Abstract: Patients with focal and generalized seizures often experience impaired consciousness that can persist into the post-ictal period. In focal limbic seizures, impaired arousal has been linked to dysfunction of subcortical arousal systems, including brainstem serotonergic (5-HT), locus coeruleus-norepinephrine (LC-NE), and basal forebrain cholinergic (ACh) pathways. Disruption of these circuits may contribute to post-ictal unresponsiveness, impaired attention and vigilance, altered cardiorespiratory function, and increased morbidity.Previous awake mice model studies demonstrate that focal limbic seizures are associated with slow-wave activity in the orbitofrontal cortex (OFC) and reduced cholinergic arousal due to inhibition and de-excitation of basal forebrain circuits. Focal seizures cause decreased multi-unit activity in the LC, but increased norepinephrine signaling is detected via spike-sorting analyses. In addition, we observed reduced single-unit activity (SUA) in the medullary raphe and variable SUA responses in the midbrain raphe during focal and focal to bilateral tonic-clonic (FBTC) seizures in rats. Based on these findings, we hypothesize that ACh, 5-HT, and NE levels in the OFC are altered in seizures due to disrupted subcortical cholinergic, serotonergic, and noradrenergic output, contributing to impaired consciousness during both ictal and post-ictal periods. Using an awake mouse model, we electrically induced focal limbic or FBTC seizures while recording hippocampal and OFC local field potentials, running and auditory-stimulated licking behavior, and pupillometry. Fiber photometry was used to measure ACh, 5-HT, and NE levels in the OFC. In focal seizures, OFC slow waves were accompanied by arrested running and licking behavior that recovered rapidly (<30 s after seizure offset). OFC ACh (10 mice) and 5-HT (7 mice) decreased, but OFC NE (4 mice) increased during and after seizures. In FBTC seizures, polyspike-wave activity was observed in the OFC along with prolonged behavioral arrest (>30 s after seizure offset). OFC ACh (5 mice) and 5-HT (7 mice) showed decreases, while NE (8 mice) exhibited an increase during and after seizures. These findings demonstrate decreased cortical ACh and 5-HT, together with increased NE, in focal and FBTC seizures. The resulting cortical state appears distinct from NREM sleep or coma and is more consistent with an encephalopathy- or delirium-like state. Future studies will examine OFC GABA and glutamate dynamics to further determine the mechanisms underlying impaired consciousness during ictal and post-ictal states and identify potential therapeutic targets.

Disclosures: J. Liu: None. **V. Doan:** None. **Y. Zheng:** None. **S. Chopra:** None. **L. Finger:** None. **J. Abraham:** None. **H. Wen:** None. **J.A. Cardin:** None. **H. Blumenfeld:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.23/O7

Topic: B.08. Epilepsy

Support: NIH/NINDS R37NS100901
NIH/NINDS F31NS149620

Title: Characterizing cortical cholinergic activity during spike and wave discharges in a mouse model of absence epilepsy

Authors: *S. CHOPRA[1], R. ASHMEADE[1], V. DOAN[1], A. BILAL[1], M. KILLORY[2], J. QU[3], Y. ZHENG[1], J. LIU[4], H. BLUMENFELD[5];
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Abstract: Absence seizures are 5 - 10 s lapses in consciousness characterized by 3-4 Hz spike-and-wave discharges (SWDs) on electroencephalography (EEG). Despite the clinical prevalence of these seizures in children, the neurochemical mechanisms underlying the transient impairment of consciousness during seizures remain poorly understood. Acetylcholine (ACh) plays a central role in cortical arousal and attention, and prior work from our lab demonstrated that reduced cholinergic output to the orbitofrontal cortex correlates with impaired consciousness during focal limbic seizures. Whether similar cholinergic dynamics occur during absence seizures has not been established. To address this, we expressed the genetically encoded ACh sensor, ACh3.0, in the orbitofrontal and barrel cortices (OFC/BC) of heterozygous *Scn8a*+/− mice, a genetic model of absence epilepsy with high SWD burden. Awake, head-fixed mice were placed on a running wheel during spontaneous seizures, with simultaneous EEG and fiber photometry recordings acquired across 39 sessions from 8 animals, totaling 2,966 seizures. ACh signals were corrected for motion and hemodynamic artifacts using the isosbestic control channel. Fiber photometry revealed consistent reductions in cortical ACh fluorescence beginning approximately 15 s prior to SWD onset and recovering gradually through the ictal period. Maximal decrease in signal in the BC (-5.8956 ± 1.3842 ΔF/F) occurred 2.63s prior to seizure onset. Post-ictal ACh fluorescence rebounded above baseline following seizure termination in both regions before returning to baseline. Pre-ictal EEG spectral analysis revealed increased low-frequency and decreased high-frequency power preceding SWD onset, replicating findings in other rodent absence models from our lab. Post-ictal spectral analysis revealed a sustained reduction in low-frequency band power persisting up to 10 s following seizure termination. These findings implicate cholinergic withdrawal as a contributor to seizure-related impairment of consciousness in absence epilepsy. Future work targeting other neuromodulators such as noradrenergic and dopaminergic pathways may yield additional mechanistic and therapeutic insights.

Disclosures: S. Chopra: None. **R. Ashmeade:** None. **V. Doan:** None. **A. Bilal:** None. **M. Killory:** None. **J. Qu:** None. **Y. Zheng:** None. **J. Liu:** None. **H. Blumenfeld:** None.

Poster

PSTR345: Seizure Networks, Circuit Dynamics, Detection, and Post-Seizure States

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.24/O8

Topic: B.08. Epilepsy

Support: NIH R01 NS066974
the Postdoctoral Research Grant from the American Epilepsy Society (1452909)

Title: Slow and Fast Dopamine Dynamics During Focal Limbic Seizures with Impaired Consciousness

Authors: *Y. ZHENG[1], J. LIU[1], J. LI[1], J. QU[1], S. CHOPRA[1], T. YADAV[1], J. A. CARDIN[2], H. BLUMENFELD[1];
[2]Dept. of Neurosci., [1]Yale Univ., New Haven, CT

Abstract: Focal limbic seizures often lead to loss of consciousness. Recent work has shown depressed cortical arousal, manifested as slow wave activity and decreased cortical acetylcholine as a possible mechanism for impaired consciousness in focal seizures. However, the role of other key subcortical arousal systems such dopamine (DA) during seizures with impaired behavioral responsiveness remains unknown. In an awake mouse model with focal limbic seizures, we measured the cortical and subcortical DA changes with fiber photometry and simultaneously assessed the arousal level with licking responses to auditory stimuli and wheel-running speed. Analyses were performed to relate fiber photometry signals and behavior. During focal limbic seizures with impaired behavioral responsiveness, we found that the cortical DA levels and the dopaminergic activity in the ventral tegmental area (VTA) increased during seizures (medial prefrontal cortex: n = 36 seizures, $p < 0.0001$; orbitofrontal cortex, n = 46 seizures, $p < 0.0001$; VTA: n = 22 seizures, $p < 0.0001$). By contrast, fast evoked DA changes at auditory click stimuli were reduced during seizures in cortical DA (medial prefrontal cortex: n = 8980 interictal clicks vs. n = 360 ictal clicks, $p < 0.05$; orbitofrontal cortex, n = 4318 interictal clicks vs. n = 284 ictal clicks, $p < 0.0001$) and VTA dopaminergic activity (n = 424 interictal clicks vs. n = 111 ictal clicks, $p < 0.0001$). Furthermore, the reduction in fast evoked dopaminergic activity changes was correlated with ictal behavioral unresponsiveness (n = 60 ictal hits vs. n = 51 ictal misses, $p < 0.001$). Together, those results reveal that unlike cortical acetylcholine decreases, cortical DA slowly increases during focal limbic seizures despite the state of depressed cortical arousal. However, fast evoked DA for external stimuli was decreased in relation to impaired responsiveness during seizures. The findings indicate that impaired consciousness during focal seizures reflects complex dysregulation of the arousal system, more closely resembling an encephalopathy-like or delirium state rather than deep sleep from a neuromodulatory perspective.

Disclosures: Y. Zheng: None. **J. Liu:** None. **J. Li:** None. **J. Qu:** None. **S. Chopra:** None. **T. Yadav:** None. **J.A. Cardin:** None. **H. Blumenfeld:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.01/P1

Topic: B.09. Glial Mechanisms

Support: NSFC82350710225
SMART D2403012

Title: Microglial PDGFB in the hypothalamic paraventricular nucleus is essential to propofol anesthesia induction

Authors: B. CAO, J. HU, H. YAO, Y. LIU, ***X.-J. SONG**;
Southern Univ. of Sci. and Technol., Shenzhen, China

Abstract: Understanding how anesthetics induce anesthesia and render the brain unconscious is fundamental to the study of general anesthesia and brain science. The overarching principle of the mechanisms of anesthesia is that anesthetics produce anesthesia by binding to specific molecular targets in central neurons, including γ-aminobutyric acid type A receptors (GABAARs), double-pore domain K^+ (2PK) channels, and N-methyl-D-aspartate receptors (NMDARs). This leads to disruption of neural activity and impairment of the integrity and function of neural circuits responsible for signal transmission and conscious perception, i.e., subjective experience. However, this hypothesis has obvious limitations. For example, some reagents that activate or block GABAARs or NMDARs, the most established targets, failed to induce anesthesia. Therefore, despite more than a century of investigation and numerous implicated processes, the specific cellular and molecular mechanisms underlying anesthesia remain elusive. The present study, we discovered that the platelet-derived growth factor subunit B (PDGFB), which is derived from microglia, plays a vital role in the induction of propofol anesthesia by regulating the activity of the potassium voltage-gated channel subfamily D member 2 (KCND2) in the paraventricular nucleus (PVN) of the hypothalamus. This process regulates the excitability of PVN glutamatergic neurons and the activity of neural circuits from PVN glutamatergic to lateral hypothalamic glutamatergic neurons. Our results demonstrate that microglia-derived PDGFB plays a more pronounced role than GABAARs in the induction of propofol anesthesia. This paradigm-shifting discovery offers a fresh perspective on the cellular and molecular mechanisms underlying the induction of anesthesia.

Disclosures: B. Cao: None. **J. Hu:** None. **H. Yao:** None. **Y. Liu:** None. **X. Song:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.02/P2

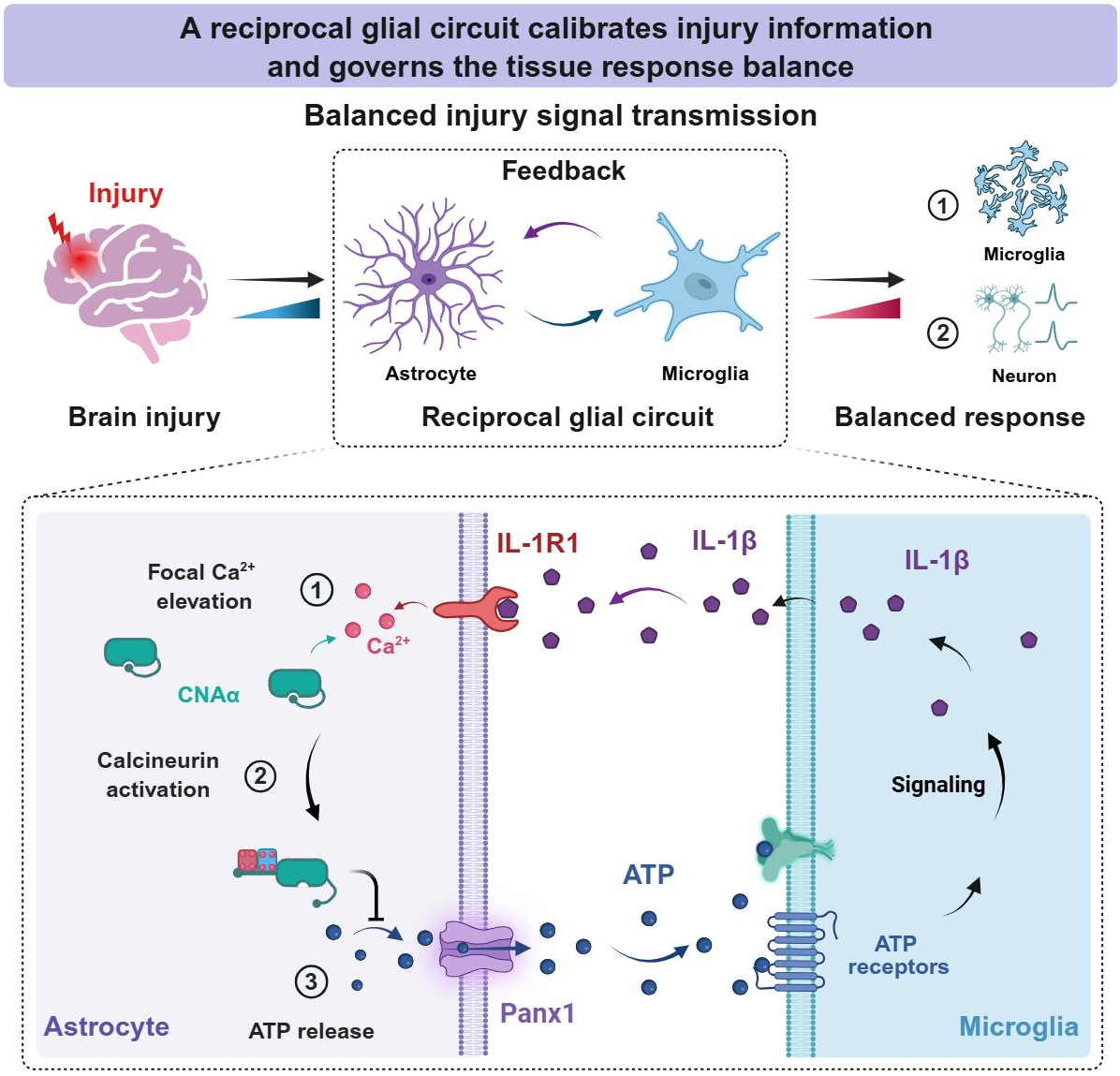
Topic: B.09. Glial Mechanisms

Support: STI2030-Major project 2021ZD0202200, subject 2021ZD0202203
National Key Research and Development program 2021YFE0116400
CAMS Innovation Fund for Medical Sciences (CIFMS) 2024-I2M-3-023

Title: A reciprocal glial circuit calibrates injury information and governs the tissue response balance

Authors: *P. LUAN[1,2,3], M. JING[1,2,3];
[1]Chinese Inst. for Brain Research, Beijing(CIBR), Beijing, China; [2]Peking university, Beijing, China; [3]Chinese Acad. of Med. Sci. & Peking Union Med. Col., Beijing, China

Abstract: Brain injury elicits complex tissue responses that must be dynamically balanced between activation and resolution, yet the mechanisms that govern this balance remain poorly understood. Using the novel genetically encoded $GRAB_{ATP1.0}$ sensor, we show that acute injury evokes focal extracellular ATP events (Inflares) with characteristic spatiotemporal signatures that scale quantitatively with injury severity, suggesting a glial mechanism for damage calibration. By selective ablating and repopulating microglia, we found that microglia exert a strong negative feedback on astrocytic Inflares, dynamically constraining their frequency, spatial spread, and temporal persistence after injury. Using P2Y12 knockout mice and chemogenetic manipulation of microglia states, we revealed that microglial feedback on astrocytic ATP release feedback is state-dependent and scales with the level of ATP signaling, suggesting that microglia continuously monitor and compute injury information to adjust tissue responses. Mechanistically, microglia-derived IL-1β acts on astrocytic IL-1 receptors and engages intracellular calcineurin signaling to suppress Panx1-dependent ATP release, establishing a molecular pathway that links injury sensing to response control. Importantly, disruption of this feedback circuit through genetic manipulation of either astrocytes or microglia destabilizes injury balance, unleashes excessive ATP signals that impairs microglial responses, disrupts neural network recovery and worsens early injury outcomes. Together, our findings identify a reciprocal astrocyte-microglia circuit that dynamically calibrates injury information and maintains tissue response balance, providing a conceptual framework for understanding injury regulation and a potential target for therapeutic intervention.



Disclosures: P. Luan: None. **M. Jing:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.03/P3

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIMH K99/R00 Pathway to Independence Grant #MH120327
NARSAD Young Investigator Grant #31308
Whitehall Foundation Grant #2022-08-051
Brain Research Foundation Seed Grant #BRFSG-2025-02

Title: Effects of inducible Tmem119-Cre expression during early postnatal development on microglia and behavior

Authors: *K. GROVE[1], S. CALL[2], J. L. BOLTON[3];
[1]Neurosci. Institute, Georgia State Univ., Atlanta, GA; [3]Neurosci. Inst., [2]Georgia State Univ. Neurosci. Inst., Atlanta, GA

Abstract: Tmem119-CreERT2 transgenic mice, which express tamoxifen-inducible Cre recombinase, are an extensively used tool for genetic manipulations in microglia. In 2022, Sahasrabuddhe and Ghosh reported adverse effects of inducible Cx3cr1-Cre expression on microglia, including decreased cell density, an activated phenotype, and upregulated phagocytic function in the developing brain, as well as anxiety-like behavior in adulthood, and highlighted a Cx3cr1-Cre toxicity specific to inducing expression in the early postnatal period. TMEM119 is expressed at lower levels in microglia, making it less likely to evoke an immune response, while also demonstrating a higher specificity to microglia, compared to CX3CR1. Prior work did not find adverse effects when employing inducible Tmem119-Cre expression; however, they did not investigate sex differences and looked at only limited brain regions (i.e., cortex), suggesting a need to further validate this genetic tool. Here, we performed confocal imaging of immunolabelled microglia in the paraventricular nucleus (PVN) of the hypothalamus, the amygdala, the parietal cortex (PC) and hippocampal subregions (CA1, CA3 and Dentate Gyrus) of Tmem119-Cre+ and Tmem119-Cre- littermates (postnatal day [P]10) following induction via tamoxifen administration (P1-3). Our preliminary data reveal increased Iba1+ microglial densities in Tmem119-Cre+/- animals in the CA1 and CA3 of the hippocampus, as well as a higher specificity of Tmem119-Cre expression to microglia in males than females in CA1, CA3, and PC. Although we find no significant differences in anxiety-like behavior in adulthood, we observed some long-lasting alterations of microglia, including a more activated phenotype in the CA3 and PC of Tmem119-Cre+/- males, but a more ramified morphology in the amygdala of Tmem119-Cre+/- males and females. Notably, we also discovered that tamoxifen administration resulted in androgenization of female genitalia, suggesting an adverse effect of administration of tamoxifen, an estrogen receptor modulator, during the perinatal critical period. The results of these experiments will have important implications for the use of the Tmem119-driven Cre/lox system to study microglia during development, and they also highlight the need to perform the correct control experiments when using these genetic tools.

Disclosures: K. Grove: None. **S. Call:** None. **J.L. Bolton:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.04/P4

Topic: B.09. Glial Mechanisms

Support: National Institute on Drug Abuse Intramural Research Program

Title: Characterization of microglia-specific cre-driver rat lines

Authors: *M. BEHERAY[1], C. RIVELL[1], B. LEE[2], J. LIU[2], H. VISHWASRAO[2], R. SVARCBAHS[1], B. K. HARVEY[1];
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Abstract: Microglia are the resident immune cell of the CNS. While acute inflammatory responses may be protective, chronic microglial activation contribute to numerous neurodegenerative conditions including, Parkinson's, Alzheimer's, multiple sclerosis, and depression. In our efforts to better understand the microglial axis of neurodegenerative conditions, we report on the development and characterization of two novel microglia-specific Cre-driver rat lines. Rat lines were generated by CRISPR-mediated knock-in of Cre into either allograft inflammatory factor 1 (Iba1) and C-X3-C motif chemokine receptor 1 (Cx3cr1) in Long Evans and Sprague-Dawley rats respectively. Both rat lines were crossed with a DIO-mCherry reporter line and aged to 6-8 weeks and 6 months for immunohistochemical analysis. Prefrontal cortex, striatum, midbrain, and hippocampus were immunolabeled for Iba1 and Cre recombinase. Colocalization of Iba1, Cre, and mCherry were obtained using a machine learning algorithm. Both rat lines had microglia-specific Cre expression with high penetrance and microglia-specific mCherry expression at 6-8 weeks and 6-month time points. To test for any gross behavioral differences in each Cre-driver line, locomotor activity was monitored over 72 hours. Iba1-iCre, Cx3cr1-iCre, and wt littermates were individually placed in locomotor chambers with a 12:12 light dark cycle. No significant differences were observed between genotypes when measuring total distance traveled and stereotypy episode counts. Additionally, due to the role of both Iba1 and Cx3cr1 in microglial immune function, transcriptomic analysis was performed. The striatum of Iba1-iCre, Cx3cr1-iCre, and wt littermates were injected with 100 ng of tumor necrosis factor-alpha (TNF- α) and contralaterally with an equal volume of saline. Tissue punches were collected 24-hours post injection and sent for poly(A) RNA-seq. There were no significant pathway changes between Cre-driver lines and wt littermates. These results support the use of both Cre-driver lines for microglia-specific expression of transgenes to further our understanding of microglia's role in physiological and pathological brain functions.

Disclosures: M. Beheray: None. **C. Rivell:** None. **B. Lee:** None. **J. Liu:** None. **H. Vishwasrao:** None. **R. Svarcbahs:** None. **B.K. Harvey:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.05/P5

Topic: B.09. Glial Mechanisms

Support: JSPS Research Fellowship for Young Scientists 25KJ0660

Title: Neuronal Micronucleus Formation in the Aging Brain and Its Impact on Microglia

Authors: *C. MAEDA[1], F. TSURUTA[2];
[1]Doctoral Program in Biology, Degree Programs in Life and Earth Sciences, Grad. Sch. of Sci.,
[2]Fac. of Life and Envrn. Sci., Univ. of Tsukuba, Tsukuba, Japan

Abstract: Microglia are the resident immune cells of the central nervous system and play essential roles in maintaining brain homeostasis throughout aging. Recent studies have demonstrated that microglia cooperate with neurons and astrocytes to regulate vascular function within the neurovascular unit. However, the mechanisms by which microglia contribute to vascular remodeling during brain aging remain unclear. Previously, we reported that neuronal micronuclei (MNs) generated during early postnatal development are transferred to microglia, thereby altering their properties. However, whether similar phenomena occur during physiological aging has remained unknown. In this study, we investigated the formation of neuronal MNs in the aging brain and examined their effects on microglia. Using NexCre; LSL-Sun1-GFP mice, we found that MNs are formed in neurons during normal aging, particularly in deep cortical layers. In contrast to developmental MNs, age-associated neuronal MNs contained little or almost no detectable DNA. Transmission electron microscopy and in vivo two-photon imaging revealed prominent nuclear envelope invaginations associated with MN formation. In addition, abnormal accumulation of nuclear B-tubulin was observed in neurons exhibiting nuclear invaginations, suggesting that cytoskeletal abnormalities contribute to age-associated MN formation. We further found that neuronal MNs were released from neurons and preferentially taken by surrounding microglia. MN-positive (MN^+) microglia exhibited elongated processes and increased process numbers, and these changes were partially suppressed by treatment with the P2Y6 receptor antagonist MRS2578. Bulk RNA-seq analysis revealed altered expression of genes involved in heparan sulfate (HS) synthesis in MN^+ microglia, including increased expression of Hs3st and Ext family genes. HS is a major extracellular matrix component involved in vascular stability and inflammatory signaling. Taken together, our findings suggest that neuronal MNs generated during aging are transferred to microglia and alter their molecular and morphological properties, potentially contributing to extracellular matrix remodeling in the aging brain. These findings reveal a previously unrecognized neuron-microglia communication pathway mediated by MN transfer during brain aging.

Disclosures: C. Maeda: None. **F. Tsuruta:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.06/P6

Topic: B.09. Glial Mechanisms

Support: NIH NIGMS GM122657

Title: Effects of sensory deprivation on microglial-associated gene expression dynamics in the mouse barrel cortex

Authors: *K. A. RIVERA GOMEZ[1,2], V. BAMWO[1], E. WILLERSON[1,2], J. C. BRUMBERG[1,2];
[1]City Univ. of New York Queens Col., Flushing, NY; [2]The Grad. Center, CUNY, New York, NY

Abstract: Sensory deprivation (SD) during the critical period alters cortical plasticity and circuitry maturation. One mechanism underlying these changes involves remodeling of perineuronal nets (PNNs), extracellular matrix structures that preferentially surround parvalbumin-positive (PV+) interneurons and regulate synaptic stability. Microglia are key regulators of neural network refinement and exhibit morphological, phagocytic, and transcriptional changes following sensory perturbations. We hypothesized that microglia contribute to extracellular matrix remodeling and experience-dependent plasticity following neonatal sensory deprivation. Here, we investigated layer- and population-level molecular changes in glial-associated genes within the barrel cortex following neonatal whisker trimming. Using RNAscope single-cell transcriptomics and immunohistochemistry, we examined expression, cell recruitment, activated subpopulation shifts, and population polarization of genes implicated in matrix remodeling. Single-cell distribution analyses revealed marker-specific expression patterns and shifts in transcriptionally distinct cellular subpopulations following sensory deprivation. Microglial-associated genes Lgmn (Legumain; matrix remodeling), Aif1/IBA1 (microglial activation), and P2ry12 (microglial homeostasis) exhibited sex-dependent changes in expression, recruitment, and activation ratios, suggesting altered microglial population states rather than a uniform inflammatory response. Aqp4 (Aquaporin 4), an astrocyte-associated gene involved in glial homeostasis and signaling, demonstrated female-specific increases in expression, recruitment, and activation ratios. Plat1 (Plasminogen Activator 1), a protease associated with PNN remodeling and PV+ interneuron development, exhibited male-specific increases in recruitment and the proportion of highly expressing cells. We also examined the heterodimeric GABA-B receptor subunits GababR1 and GababR2, which regulate inhibitory neurotransmission and circuit stability, and observed a female-specific increase in GababR2 expression, recruitment, and activation ratio following sensory deprivation. Together, these findings reveal sex-dependent shifts in glial-associated transcriptional states following neonatal sensory deprivation that are consistent with extracellular matrix remodeling in the barrel cortex. The results support a role for microglia and broader glial interactions in experience-dependent plasticity during early cortical development.

Disclosures: K.A. Rivera Gomez: None. **V. Bamwo:** None. **E. Willerson:** None. **J.C. Brumberg:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.07/Q1

Topic: B.09. Glial Mechanisms

Support: NIH F31DE035400
NIH BRAIN R01NS110564
NIH R01NS136622
NIH R01MH106460

Title: Microglia Data Refinement: An automated MATLAB pipeline for high dimensional microglia morphological analysis

Authors: *S. L. NARAYANAN[1], A. K. GORMALEY[1], C. PRESZLER[1], A. VAZQUEZ[2], T. CUI[3];
[1]Bioengineering, [2]Radiology, [3]Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Rationale: Microglia exhibit distinct morphological states that reflect their functional roles. Accurately classifying microglial activation states could be groundbreaking for diagnosing neurodegenerative diseases and evaluating neural implant biocompatibility. Traditional characterization of microglia morphology involves manual tracing of individual cells and is slow and subjective. Advanced image processing software allow for some automation but still require heavy manual review. With the lack of high volumes of data and manual classification, morphological characterization of microglia is often limited to simple binary classifications based on ramification. However, it is becoming increasing well known through high dimensional morphological analysis as well as advanced transcriptomic and other techniques that microglia exhibit more complex functional roles that manifest in diverse morphological phenotypes. **Objective:** To establish a microglia morphological analysis pipeline that is entirely automated, high dimensional, easy to use, and open source. **Methods & Results:** Iba-1 images taken from animals with microelectrode array implants were flattened and hist-matched to ensure even sampling of microglia within each image and across all images. DAPI images were used to assign Iba-1 signal to cell-nuclei. Individual microglia were converted into a cell body + skeletonized processes. 18 features including soma characteristics and Sholl analysis-based process characteristics were extracted from each cell. This work is presented as a package of code freely available for download from GitHub. For our case study of chronic (4 week) vs acute (4 day) MEA implant, we produced a multidimensional feature set of microglia from all these images. The data was reduced using principal component analysis (PCA) and clustered using a gaussian mixture model (GMM). We identified 4 clusters which were given tentative functions based on their morphological features: homeostatic, activated and surveilling, migrating, and phagocytic. In the acute implanted tissue, we observed high levels of the activated and surveilling microglia, migration across the whole brain, and high numbers of phagocytic microglia. In the chronic implanted tissue, we observed a return to the homeostatic state particularly in contralateral tissue with some continued elevated phagocytosis.

Disclosures: S.L. Narayanan: None. **A.K. Gormaley:** None. **C. Preszler:** None. **A. Vazquez:** None. **T. Cui:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.08/Q2

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01NS117585
NIH Grant R01NS123154

Title: Disease-associated epigenetic dysregulation disrupts human microglial homeostasis in a chimeric mouse model

Authors: ***J. WU**[1], K. WETTSCHURACK[2], X. CHEN[3], J. ZHANG[3], C. YUAN[4], L.-J. WU[5], Y. YANG[3];
[1]Prudue Univ., West Lafayette, IN; [2]MCMP, Purdue Univ., Lafayette, IN; [3]MCMP, [4]Purdue Univ., West Lafayette, IN; [5]Neurol., Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Stable epigenetic regulation is important for maintaining microglial identity and function, but how disease-associated epigenetic defects affect human microglia in vivo is not well understood. Here, we generated human iPSC-derived microglial progenitor cells carrying a disease-associated mutation in an epigenetic regulator and transplanted them into neonatal recipient mice to generate human microglia chimeric mice. After long-term engraftment, mutant human microglia were compared with control human microglia in the chimeric brain. Epigenetically altered human microglia showed reduced homeostatic features, increased lysosomal and phagocytic activity, and accumulation of intracellular debris-like material. These changes were accompanied by aging-like cellular phenotypes and were also observed in iPSC-derived microglia in vitro. Our findings suggest that disease-associated epigenetic dysregulation is sufficient to disrupt long-term human microglial homeostasis and may contribute to microglia-mediated CNS vulnerability.

Disclosures: J. Wu: None. **K. Wettschurack:** None. **X. Chen:** None. **J. Zhang:** None. **C. Yuan:** None. **L. Wu:** None. **Y. Yang:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.09/Q3

Topic: B.09. Glial Mechanisms

Support: NIH Grant MH113257

Title: Spatial statistics and point pattern analysis reveal lifespan trajectories of microglial density and clustering in the primate hippocampus.

Authors: *A. NUSIR[1], C. MARTINEZ CARDENAS[2], J. I. ARELLANO[4], A. DUQUE[5], N. KABBANI[3];
[1]Interdisciplinary Program in Neurosci., [3]Sch. of Systems Biol., [2]George Mason Univ., Fairfax, VA; [4]Neurosci., Yale Univ., New Haven, CT; [5]Neurosci., Yale Univ. Sch. Med., New Haven, CT

Abstract: The hippocampus undergoes substantial structural remodeling across the lifespan, yet how its resident immune cells, microglia, reorganize during development and aging remains poorly understood in primates. We quantified microglial density and spatial organization across hippocampal subfields in 15 female rhesus macaques spanning late gestation (gestational day 140) to advanced age (32.4 years) using tissue from the MacBrain Resource Center. Animals were grouped as perinatal (GD140-7 days postnatal), postnatal (2.5-6 months), juvenile/adult (11.4 months-9.8 years), and aged (18.7-32.4 years). Microglial density exhibited a U-shaped trajectory, declining during early postnatal life before increasing through adulthood and aging, with the dentate gyrus showing the greatest age-related change. Nearest-neighbor distance followed an inverse pattern, indicating maximal microglial dispersion during the postnatal period. Ripley's H-function analysis revealed age-dependent alterations in microglial territorial organization, including an expanded exclusion radius in aged animals. Tile-based spatial analyses further identified increased microglial clustering within CA1 in the aged group. In the oldest animal, regions of microglial clustering corresponded with amyloid-β and phosphorylated tau immunoreactivity. Together, these findings demonstrate dynamic lifespan-dependent remodeling of microglial spatial organization and establish a quantitative framework for studying neuroimmune architecture in the aging primate hippocampus.

Disclosures: A. Nusir: None. **C. Martinez Cardenas:** None. **J.I. Arellano:** None. **A. Duque:** None. **N. Kabbani:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.10/Q4

Topic: B.09. Glial Mechanisms

Support: Nu Rho Psi Undergraduate Research Grant

Title: Examining the localization of CB1Rs in microglia in the lateral hypothalamus

Authors: *M.-C. COCKERHAM[1], D. A. MITRANO[2];
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Abstract: Alzheimer's disease neurodegeneration is exacerbated by oxidative stress in the brain. As a result, therapies targeting core inflammation are of utmost importance. Microglia are of interest to Alzheimer's research due to their role in neuroinflammation. Cannabinoids bind to two G-Protein Coupled Receptors (GPCRs), CB1 and CB2. CB1, primarily located throughout the central nervous system, is the target of Δ9-THC, the main psychoactive ingredient in cannabis. Located throughout the cerebral cortex, CB1 receptors are also densely concentrated in the hippocampus, amygdala, basal ganglia, hypothalamus, and cerebellum. Phytocannabinoids consist of a specialized group of metabolites first discovered in Cannabis sativa. This includes both Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD). These phytocannabinoids act upon the endocannabinoid system in mammals to modulate involuntary functions such as breathing, pain reception, digestion, and sleep-wake cycles. To gain an understanding of the relationship between microglia and cannabinoid receptors, we will label mouse tissue with an antibody for the CB1R and Iba-1, a marker of microglial cells. We will specifically be examining the lateral hypothalamus, a brain area associated with autonomic bodily functions. This project aims to determine the presence and possible colocalization of CB1Rs with Iba-1 in untreated animals. This can be used in future studies to determine whether the same pattern of localization exists in mouse models of Alzheimer's disease.

Disclosures: M. Cockerham: None. **D.A. Mitrano:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.11/Web Only

Topic: B.09. Glial Mechanisms

Support: Studies were supported by the National Science Center JPND 2022/04/Y/NZ5/00122.

Title: How do various components of the enriched environment affect transcriptomic responses and anathomy of microglial cells?

Authors: *K. SZYDLOWSKA[1], M. FLORCZYK[3], R. TIVANELLO[2], Z. LUCZAK-SOBOTKOWSKA[1], A. J. HANNAN[4], R. PAOLICELLI[5], A. JAWAID[6], B. KAMINSKA[7]; [1]Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland; [2]Nencki Inst. of Exptl. Biol. PAS, Warszawa, Poland; [3]Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland; [4]Florey Inst. of Neurosci. and Mental Health, Univ. of Melbourne, Melbourne, Australia; [5]Systems and Cell Biol. of Neurodegeneration, Univ. of Zurich, IREM, Schlieren, Switzerland; [6]Knowledge Base Lukasiewicz Port, Wroclaw, Poland; [7]Nencki Inst. of Exptl. Biol., Warsaw, Poland

Abstract: Environmental enrichment (EE) is an experimental paradigm that combines physical, sensory, and cognitive stimulation and shows beneficial effects in pre-clinical models of neurodegeneration. Microglia are resident myeloid cells of the central nervous system (CNS),

which, through bidirectional communication with other brain cells, maintain CNS homeostasis. EE partially reversed the pro-inflammatory effects of aging on microglia and attenuated the inflammatory response of microglia to Aβ oligomers, thereby promoting their cytoprotective and phagocytic phenotypes. In this study, we investigated the transcriptomic responses of microglia to EE or its individual components. Mice (male and female) were subjected to the full EE or EE without physical exercise, EE without cognitive stimulation, EE without social engagement (single housing of mice); naïve mice or mice single housed without EE were used as controls. Microglia from hippocampi were immunosorted as CD11b+ cells by flow cytometry and subjected to RNA sequencing and computational analyses. Principal component analysis did not show significant transcriptomic differences between groups in females; however, distinct transcriptomic patterns emerged between various groups in males. We identified the gene signature associated with EE, which was, to a large extent, induced by physical activity. Gene Ontology (GO) analyses revealed various processes induced by specific EE components, distinct from those of a full EE. Interestingly, stress caused by solitary housing abrogated EE-induced gene expression in microglia. We also performed a detailed analysis of cellular morphology in different conditions to visualise any potential changes in microglia activation dependent on the environmental enrichments. Our results demonstrate specific microglial responses to a full EE protocol, as well as its different components, shedding light on which elements enhance the protective and modulatory role of microglia.Studies were supported by the National Science Center JPND 2022/04/Y/NZ5/00122.

Disclosures: K. Szydlowska: None. **M. Florczyk:** None. **R. Tivanello:** None. **Z. Luczak-Sobotkowska:** None. **A.J. Hannan:** None. **R. Paolicelli:** None. **A. Jawaid:** None. **B. Kaminska:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.12/Q5

Topic: B.09. Glial Mechanisms

Support: R01NS125074
R01AG083164
1F31NS129204-01A1
S10OD030402

Title: Inhibition of TGF-beta Signaling in Microglia Stimulates Hippocampal Adult Neurogenesis and Reduces Anxiety-Like Behavior in Adult Mice

Authors: *J. YAZELL[1], K. WARE[2], A. TARANOV[3], A. M. BEDOLLA[4], C. THAPA[6], S. A. LIDDELOW[7], A. LUO[5];
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[5]Mol. and Cell. Biosci., [3]Univ. of Cincinnati, Cincinnati, OH; [6]Ctr. for Psychiatric Genet., Endeavor Hlth., Evanston, IL; [7]Neurosci. Inst., NYU Grossman Sch. of Med., New York, NY

Abstract: Adult neurogenesis in the subgranular zone (SGZ) has been implicated in cognitive and affective functions. The role of neuroinflammation and reactive microglia in SGZ neurogenesis is not well understood. TGF-β signaling is critical to maintaining microglia homeostasis in the adult brain. To investigate the role of microglia in SGZ neurogenesis, using microglia-specific inducible knockout (iKO) mice for TGF-β1 ligand or receptor (*Alk5* or *Tgfbr2*), here we show that TGF-β-deficient microglia increase adult neurogenesis in the SGZ, accompanied by altered anxiety-like behavior in KO mice. Single-cell RNAseq (ScRNAseq) analysis shows decreased PTEN signaling, and immunohistochemistry shows increased mTOR activity in DCX+ newly born neuroblasts at the SGZ in iKO mice. Inhibition of mTOR signaling by rapamycin reverses the heightened SGZ neurogenesis in iKO mice. This study reveals the role of microglia in regulating hippocampal adult neurogenesis via the PTEN-mTOR pathway and its potential implications for behavioral and affective functions.

Disclosures: J. Yazell: None. **K. Ware:** None. **A. Taranov:** None. **A.M. Bedolla:** None. **C. Thapa:** None. **S.A. Liddelow:** None. **A. Luo:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.13/Q6

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Near-simultaneous Recording of Two-photon Imaging and Fast-scan Cyclic Voltammetry

Authors: *E. S. RAMSSON[1], J. T. YORGASON[2];
[1]Grand Valley State Univ., Allendale, MI; [2]Translational Neurosci., Wake Forest Univ. Sch. of Med., Winston-Salem, NC

Abstract: The immune system regulates neuronal activity through complex mechanisms that involve cytokine/chemokine release, chemoattraction, and trogocytic pruning of overactive synapses. The ventral striatum is a region heavily involved in associative learning, modulated by dopamine signalling. How this circuit, including local dopamine release, is regulated by local immune cells remains unexplored. Multi-photon microscopy is a powerful technique that enables the live imaging of highly motile cells including microglia. Fast-scan cyclic voltammetry (FSCV) permits subsecond measurements of dopamine changes. To date, these transformative techniques have never integrated. To this end, we validate the near-simultaneous collection of two-photon (2P) imagery of fluorescently-labeled microglia and electrically stimulated dopamine release and uptake in the nucleus accumbens of mouse brain slices. We reveal that a 4 hour FSCV experiment (4ms, 30µA, single pulse) proves insufficient to induce microglia recruitment/accumulation, yet reliably produces detectable dopamine transmission. Similarly, a 4

hour LTP stimulus paradigm (100Hz, 100 pulse, 30μA) did not produce accumulation, and produced mixed effects on dopamine transmission, demonstrating that electrical stimulations do not produce uniform changes in microglia mobilization. These data strongly suggests that any experimental sequences triggering microglia, such as drugs of abuse exposure, function independent of the FSCV experimental setup, and support the use of electrical stimulation studies for electrophysiology research. Future experiments will examine fine microglia morphology changes and relate evoked changes to dopamine transmission measures.

Disclosures: E.S. Ramsson: None. **J.T. Yorgason:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.14/R1

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant P50AA017823
NIH Grant R01AA030469

Title: Distinct functional and morphological features of hippocampal microglia between adolescents and adults

Authors: *D. GERACI[1], A. S. VORE[2], T. DEAK[3];
[1]SUNY - Binghamton Univ. Behavioral Neurosci., Binghamton, NY; [2]Binghamton Univ., Binghamton, NY; [3]Behavioral Neurosci. Program, Dept. of Psychology, Binghamton University-SUNY, Binghamton, NY

Abstract: The neuroimmune system continues to mature during adolescence, which may contribute to age differences in stress sensitivity. Activation of the HPA axis and subsequent glucocorticoid release is known to affect the neuroimmune system via nuclear translocation of glucocorticoid receptors (GR), and downstream transcriptional activation of NFκB-related genes. However, induction of IL-6 and IκBα gene expression, two representative neuroimmune genes controlled by GR transactivation, were significantly reduced in adolescents relative to adults following either immune challenge or acute GR agonism with dexamethasone (DEX). The goals of the present experiments were to assess age differences in IL-6 and IκBα protein expression following DEX administration, and to explore the mechanisms underlying adolescent neuroimmune immaturity. Male adolescent (P28-32) and adult (P82-91) Sprague Dawley rats were administered acute DEX (50, 250, or 500 μg/kg; s.c.) or vehicle (50% propylene glycol, 50% saline), and tissue was collected 4 hours later for immunofluorescence. Firstly, IL-6 and IκBα protein expression were quantified and colocalized with GFAP and tomato lectin in the hippocampus to evaluate age and cell-type localization differences in dexamethasone-induced cytokine expression. Adolescents showed greater IL-6 and IκBα protein expression relative to adults, and DEX significantly reduced expression of both proteins in adolescents only. Secondly,

as ligand-bound GR will translocate to the nucleus and promote neuroimmune gene transcription, age differences in GR nuclear translocation were explored as a potential mechanism of blunted adolescent neuroimmune sensitivity. Immunofluorescent labeling of GR, NeuN, and DAPI were used to quantify nuclear and cytosolic localization of GR, however, no age or group differences were seen in GR nuclear translocation. Finally, as microglia are largely responsible for coordinating neuroimmune responses, we evaluated age differences in microglia morphology using immunofluorescence and confocal microscopy. Adolescents displayed greater numbers of microglia in the hippocampus, however, adults showed greater branch depth, branch length, and sholl intersections. Therefore, age differences in both the quantity and morphology of microglia may explain functional differences in the adolescent and adult neuroimmune responses that are regulated by glucocorticoids.

Disclosures: D. Geraci: None. **A.S. Vore:** None. **T. Deak:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.15/R2

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

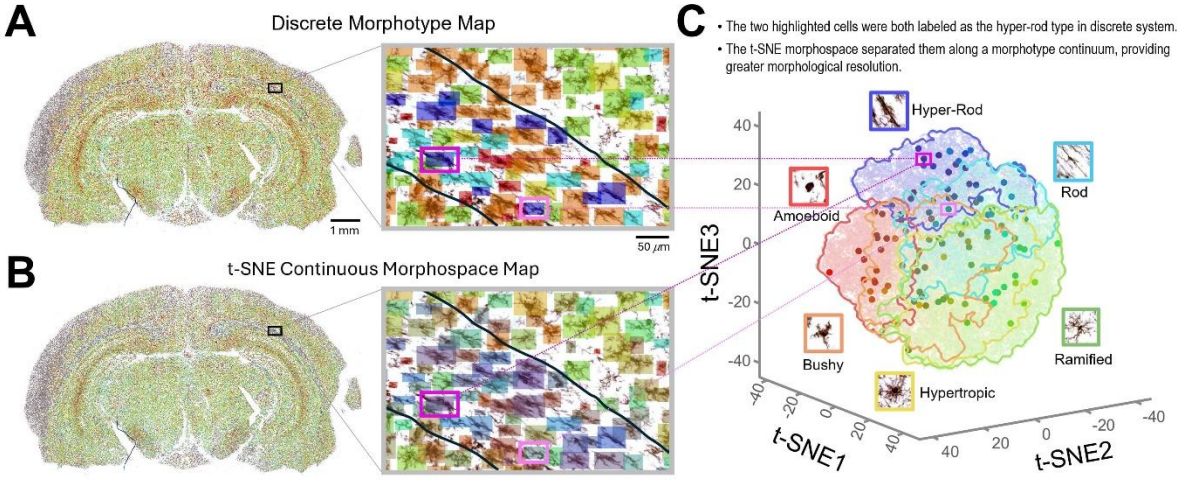
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CZI NDCF award

Title: Extending StainAI to Continuous Microglial Morphology Mapping Using Validated 3D Morphospace

Authors: *C.-H. HSU[1], B.-M. CHANG[1], D.-Y. LIU[1], M. SHIH[1,2], H. ZEHRA[1], S. ALI[1], H.-J. CHUANG[1,3], Y.-A. LIAO[1,4], E.-A. ETTE[5,1], S. LIN[1], T.-R. TU[1], Y.-Y. HSU[2], M. SHOYKHET[6], P. WANG[1,7], T.-W. TU[1,8];
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Abstract: Microglial morphology provides an accessible readout of neuroinflammation in brain injury and disease. Our previous deep learning-based StainAI framework enabled high-

throughput analysis of Iba1-stained sections by identifying individual microglia and assigning morphotype labels from resting-like to activation-associated phenotypes. While these discrete labels are easy to interpret, they can be ambiguous when cells exhibit intermediate or mixed morphologies that fall between classes. This study introduced a 3D t-SNE-based analysis to extend the discrete morphological framework into a continuous spectrum, facilitating identification of transitional microglial morphologies after cardiac arrest. A 3D t-SNE morphospace was constructed from 25 morphometric features extracted from 420,574 cerebrum microglia obtained from a developing rat model of asphyxial cardiac arrest. Each microglial cell was assigned a continuous color based on its position within the t-SNE morphospace, with color references anchored to the six StainAI morphotypes. Figure 1 compares morphology maps derived from discrete classification (Fig. 1A) and continuous morphospace (Fig. 1B). Continuous morphospace maps replaced abrupt class boundaries with smooth color gradients, for example in the external capsule, where neighboring cells exhibited mixed or borderline morphologies (Fig. 1A, B). These cells formed a continuous distribution within the morphospace, with gradual color transitions between neighboring classes. In contrast, discrete classification grouped them into the same morphotype (Fig. 1C). In injured brains, morphological change can be quantified as the distance between a test sample and its corresponding control reference point within the morphospace. Our results suggest that 3D t-SNE morphospace extends discrete classification into a continuous spectrum while preserving interpretability of microglial activation states. This enables detection of subtle neuroinflammatory cues and supports studies of disease mechanisms and therapeutic discovery.



Disclosures: C. Hsu: None. **B. Chang:** None. **D. Liu:** None. **M. shih:** None. **H. Zehra:** None. **S. Ali:** None. **H. Chuang:** None. **Y. Liao:** None. **E. Ette:** None. **S. Lin:** None. **T. Tu:** None. **Y. Hsu:** None. **M. Shoykhet:** None. **P. Wang:** None. **T. Tu:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.16/R3

Topic: B.09. Glial Mechanisms

Support: Chan Zuckerberg Initiative
Helis Foundation
Kleberg Foundation

Title: Skoupocytosis: a role for homeostatic microglia in neuronal proteostasis

Authors: *R. PEPPER[1], J. GRISWOLD[2], F. MIDDLETON-DAVIS[4], L. TRAN[4], D. E. BERGLES[5], Y. IMOTO[6], S. WATANABE[3];
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Abstract: Neuronal proteostasis is fundamental to sustain function in all compartments of the neuron. Historically proteolytic organelles, even from distal processes, are thought to be sent back to the cell body for degradation. We observed large proteolytic organelles to be stationary in cultured neurons. However upon addition of microglia these neuronal proteolytic organelles were taken up from synapses, axons, dendrites and somas. We named this process 'skoupocytosis' after the Greek word for garbage, *skoupidia*. Skoupocytosis is exceptionally precise, as microglia engage in the excision of proteolytic organelles without disrupting the functional vesicle pool of synapses as observed in the Allen Institute for Brain Science's electron microscopy 3D reconstruction of the mouse neocortex. To explore this phenomenon, we fluorescently tagged HRS, an ESCRT0 protein recruited in the initial phase of proteolytic organelle formation. Using correlative electron microscopy, we confirmed HRS localized to the large stationary organelles observed in culture as autophagosomes and amphisomes. Using proteomics from isolated synaptosomes we found ABHD16a, a Phosphatidyserine (PS)-specific phospholipase, which converts PS into lyso-PS, was enriched at synapses after hyperexcitability. PS is a major component of the plasma membrane residing on the inner leaflet, however can be flipped externally to act as a spatial cue for microglia engagement. Given this we hypothesized that as PS accumulates on the surface of proteolytic organelles containing synapses and is cleaved by ABHD16a to generate lyso-PS. Using super-resolution imaging we found 98% of HRS is associated with ABHD16a in brain slices. Using a small molecule inhibitor of ABHD16a KC01 we observed more externalized PS adjacent to HRS organelles, and in acute brain slices reduces the amount of HRS internalized by microglia, resulting in accumulation of HRS outside of microglia. In summary, we have identified a new homeostatic function of microglia to remove of proteolytic organelles from neurons. Skoupocytosis provides a convenient avenue for neurons to ensure protein homeostasis is maintained even in inaccessible compartments of the neuron, and during times of high proteolytic demand such as high frequency firing and aging.

Disclosures: R. Pepper: None. **J. Griswold:** None. **F. Middleton-Davis:** None. **L. Tran:** None. **D.E. Bergles:** None. **Y. Imoto:** None. **S. Watanabe:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.17/R4

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01GM134104

Title: The Arp2/3 complex maintains mitochondrial integrity and redox health in microglia

Authors: *I. SWAFFORD[1], J. ROTTY[2];
[1]Uniformed Services Univ. of Hlth. Sci. Grad. Program In Neurosci., Bethesda, MD; [2]Dept. of Biochem., Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Microglia are widely considered to be major players in the onset and development of neurodegenerative diseases, becoming immunologically primed for activation with demonstrable mechanical and metabolic deficits. However, very few studies to date have examined the interplay between mechanical and immunometabolic defects in microglia, and none in the context of aging and neurodegeneration. Notably, actin cytoskeleton dysfunction in peripheral immune cells is known to drive mechanical defects in addition to immune pathologies, including hyperactivation and the senescence-associated secretory phenotype (SASP). Additionally, the actin cytoskeleton is known to maintain integrity of organelles such as mitochondria, where its disruption may drive immunological defects as well as dysmetabolism. Thus, we predict that microglia, as the resident immune cell of the central nervous system, will similarly adopt a dysfunctional immunometabolic phenotype upon disruption of the actin cytoskeleton. One particular cytoskeleton candidate, the Actin-related protein 2/3 (Arp2/3) complex, governs phagocytosis, regulates organellar integrity, and contains downregulated components in aged microglia. Here, we show that following inhibition of the Arp2/3 complex, mitochondrial integrity is impaired, followed by generation of ROS and lipid droplets. Future studies will examine the metabolic state of the cell through Seahorse assays, innate immune activation, and presence of mitochondrial dsDNA as a consequence of impaired mitochondrial integrity.

Disclosures: I. Swafford: None. **J. Rotty:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.18/R5

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: HHMI NoRIC

Title: The role of microglia in capillary tone and sensory behavior following respiratory inflammation

Authors: *M. E. DOCETI[1], U. B. EYO[2];
[1]Microbiology, Immunology, and Cancer, [2]Neurosci., Univ. of Virginia, Charlottesville, VA

Abstract: Adults experience 2-4 respiratory infections per year, yet their acute and long-term neurological consequences are poorly understood. Brain function depends on neurovascular coupling, the communication between neurons and the vasculature, which can be disrupted during severe or prolonged respiratory inflammation. Microglia, the brain's first line of defense against invading pathogens, control inflammation responses in the brain and are known to regulate capillary diameter and blood flow during homeostasis. However, how microglia react to a respiratory immune stimulus to alter blood flow and change neuronal activity are poorly understood. To address this question and model respiratory inflammation, we utilize a 1mg/kg lipopolysaccharide (LPS) injected intratracheally (IT) into c57b6 mice, a technique previously used to cause acute lung injury. IT-LPS mice lose a peak amount of weight (~5 - 10%) at 24 hours and slowly recover back to 100% starting weight by 7 days. At the peak 24 hour timepoint, we used immunofluorescence staining in the somatosensory cortex and Sholl analysis to detect microglia morphological changes indicative of activation and microglia-capillary decoupling. Further, using in-vivo two-photon imaging and red blood cell flux analysis, we saw deficits in blood flow in that same region of the brain. Finally, to correlate our fixed tissue and in-vivo imaging studies in the somatosensory cortex with relevant behavior, we utilized the whisker nuisance assay as a measure of hypersensitivity. With this test, we find altered burrowing activity in response to whisker stimulation at 24 hours that lasts up to 7 days, suggesting that the mice altered sensitivity to the stimulus. Thus, we find that IT-LPS can model the effects of a respiratory infection that can lead to somatosensory changes in the brain. More specifically, we find that there are microglial and vascular alterations that might lead to the downstream changes in somatosensory processing, though more work must be done to show causation. Together, these findings suggest that acute respiratory inflammation disrupts neurovascular homeostasis and provide a foundation for investigating how microglia contribute to blood flow deficits and behavioral alterations following respiratory immune challenge.

Disclosures: M.E. Doceti: None. **U.B. Eyo:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.19/R6

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: AHA postdoc fellowship (26POST1560008) (J.Z.)

Title: Vessel-Associated Microglia Preserve Vascular Integrity in Tumor-Bearing Brains

Authors: *J. ZHENG[1], R. HUA[1], A. J. JOHNSON[2], L.-J. WU[1];
[1]UT Hlth. Houston, Houston, TX; [2]Immunol., Mayo Clin., Rochester, MN

Abstract: Microglia are the resident immune cells of the central nervous system and have been classically studied in the context of neuroinflammation. Vessel-associated microglia (VAM) are a specialized subset whose somata directly contact capillaries and account for approximately 30% of microglia in the naïve brain. Although VAM have recently been recognized as regulators of cerebral blood flow and blood-brain barrier integrity, their role in pathological vascular remodeling remains largely unclear.
Here, we used glioma models in which peritumoral capillaries undergo extensive vascular remodeling and blood-brain barrier dysfunction, providing an in vivo platform for studying capillary vulnerability and vascular stability. Our study combined transgenic mouse tools with state-of-the-art longitudinal in vivo two-photon imaging, together with behavioral assessment, survival analysis, T2-weighted magnetic resonance imaging, and immunostaining, to investigate the role of VAM in peritumoral vascular remodeling and stability.
We found that the peritumoral region contained dense capillary networks and a marked increase in VAM, which accounted for more than 60% of the total myeloid cell population. Genetic lineage tracing confirmed that these cells were microglia. Longitudinal two-photon imaging of microglia-capillary interactions revealed that VAM exhibited an elongated, vessel-wrapping morphology. A similar response was observed following single-vessel photothrombosis, suggesting that VAM recruitment and vessel wrapping represent a response to capillary injury.
We next used a CSF1R inhibitor to deplete microglia. Strikingly, more than half of the microglia-depleted, tumor-bearing mice developed acute, lethal paralysis by day 15, whereas control tumor-bearing mice remained asymptomatic at this time and survived for approximately 30 days. T2-weighted MRI of mice that developed acute paralysis revealed extensive intracranial hemorrhage and severe edema, while two-photon imaging showed nodular and abnormal vasculature at the onset of paralysis.
Together, our findings identify VAM as critical neurovascular stabilizers that preserve peritumoral capillary integrity and protect against lethal hemorrhage in glioma. These results reveal an essential role for immune cells in maintaining brain vascular homeostasis and raise important safety considerations for CSF1R-targeted therapies in the diseased brain.

Disclosures: J. Zheng: None. **R. Hua:** None. **A.J. Johnson:** None. **L. Wu:** None.

Poster

PSTR346: Microglia Biology

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.20/S1

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Optical pooled CRISPR screen allows parallel single-cell morphological, proteomic, and perturbation profiling in human iPSC-derived ioMicroglia

Authors: T. PERLOVA[1], N. VINKO[2], **A. TUCKER**[3], I. VICENTE-GARCIA[1], N. PAPAI[1], C. NEUMAYR[1], M. GAMPERL[1], S. BARBARIA[1], *A. ARMESILLA[3], T. BUERCKSTUEMMER[1], S. SALIC-HAINZL[1];
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Abstract: Targets with human genetic evidence are twice as likely to succeed in clinical trials and gain drug approval compared to those without (Nelson et al., Nature Genetics, 2015). Identifying and validating such targets requires systematic approaches that can connect genetic perturbations to complex cellular phenotypes in physiologically relevant models. To address this, we have developed fully characterised, scalable, and physiologically accurate iPSC-derived cellular models. By engineering these to be CRISPR-ready, we enable precise genetic perturbations across multiple cell types, including ioGlutamatergic Neurons, ioMotor Neurons, ioMicroglia, and ioOligodendrocytes. These platforms facilitate pooled CRISPR activation (CRISPRa), interference (CRISPRi), and knockout (CRISPRko) screens paired with diverse readout modalities. From viability and functional assays to single-cell transcriptomics (scRNA-seq), our workflow captures distinct dimensions of cellular biology.To further expand the versatility of our CRISPR screening platform, we have integrated imaging-based readouts by running an optical pooled CRISPR screen (OPS). Using CRISPR-Ready ioCells and the Element Biosciences AVITI24 system, we demonstrate in situ co-detection of sgRNA identity, protein abundance, and morphological features within a single experiment. As a proof-of-concept, we performed a screen in human iPSC-derived ioMicroglia, linking genetic perturbations to morphological and proteomic changes associated with microglial activation, demonstrating the ability of OPS to capture multiple dimensions of cellular phenotypes in pooled CRISPR screens. This CRISPR screening platform provides an end-to-end workflow for target discovery and validation, moving seamlessly from perturbation to mechanism to functional effect to enable the scalable dissection of human neural disease.

Disclosures: T. Perlova: A. Employment/Salary (full or part-time):; Bit Bio Discovery. **N. Vinko:** A. Employment/Salary (full or part-time):; Myllia. **A. Tucker:** A. Employment/Salary (full or part-time):; bit bio. **I. Vicente-Garcia:** A. Employment/Salary (full or part-time):; Bit Bio Discovery. **N. Papai:** A. Employment/Salary (full or part-time):; Bit Bio Discovery. **C. Neumayr:** A. Employment/Salary (full or part-time):; Bit Bio Discovery. **M. Gamperl:** A. Employment/Salary (full or part-time):; Bit Bio Discovery. **S. Barbaria:** A. Employment/Salary (full or part-time):; Bit Bio Discovery. **A. Armesilla:** A. Employment/Salary (full or part-time):; bit bio ltd. **T. Buerckstuemmer:** A. Employment/Salary (full or part-time):; Bit Bio Discovery. **S. Salic-Hainzl:** A. Employment/Salary (full or part-time):; Bit Bio Discovery.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.01/S2

Topic: B.10. Neuro-Oncology

Title: Contrast-enhanced MRI as a tool for monitoring blood-brain barrier leakage in an orthotopic U-87 MG rat model

Authors: R. IMMONEN, ***J. RYTKÖNEN**, T. HUHTALA;
IQVIA Labs. Finland Oy, Kuopio, Finland

Abstract: Gliomas are the most common type of primary brain tumors and are known to disrupt the blood brain barrier (BBB), mainly due abnormal angiogenesis and endothelial dysfunction due to inflammation and oedema. Magnetic resonance imaging (MRI) offers unprecedented soft tissue contrast, high spatial resolution and enables longitudinal monitoring in a fully translational manner. In addition to monitor tumor growth, cerebral blood flow (CBF) and leakage of BBB can be measured using a contrast enhancing agent. In this study the BBB leakage was measured longitudinally alongside tumor growth in a rat model of orthotopic glioma.
Total of 10 SRG rats (Sprague Dawley-Rag^{2em2hera}Il2rg^{em1hera}/HblCrl, Charles River) underwent intracranial stereotaxic surgery into the right striatum; 8 were implanted with U-87 MG cells ($1x10^5$), and 2 received vehicle as sham controls. MRI imaging was performed on D7, D11 D16 and D21 after the tumor implantation with 11.7 T horizontal small-animal scanner (Bruker BioSpin, Germany). The imaging consisted of quantifying tumor volumes from T2-weighted MRI and assessment of tumor perfusion and BBB permeability using T1-weighted images gadolinium (Gd) contrast (Dotarem, 1 mL/kg, i.v). Finally, brain samples were collected for immunohistochemical (IHC) staining of proliferating cells (Ki67) and vascular cell adhesion (CD31).
The average tumor volume reached an average of 247 ± 95 mm^3 (mean ± SD, n=8) in three weeks. Tumor core and rim were determined based on the first-pass enhancement in the contrast-enhanced imaging. The rim was outlined by delayed enhancement corresponding to neovascularized tissue. IHC staining confirmed only moderate proportion of Ki67-positive cells to total cell density, which was consistent with late-stage tumor tissue where the tumor has grown beyond its blood supply, leading to hypoxic and necrotic regions.
As a conclusion, BBB permeability and perfusion were characterized across different regions and states of growth in orthotopic glioma model using contrast enhanced MRI.

Disclosures: R. Immonen: A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **J. Rytkönen:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **T. Huhtala:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.02/S3

Topic: B.10. Neuro-Oncology

Title: Temporal dynamics of inflammatory blood markers reveal distinct prognostic groups and enable the early detection of progression of glioblastoma

Authors: *S. AWASTHI[1], V. SANKER[2], M. LIM[2];
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Abstract: Glioblastoma (GBM) is the most common primary brain tumor in adults and carries a poor prognosis, with a median survival of 14-15 months and fewer than 6% of patients surviving beyond 5 years. GBM prognostication largely relies on static baseline measurements without factoring in the dynamic evolution of systemic inflammation during disease progression. We analyzed longitudinal trajectories of multiple inflammatory blood markers from 869 patients with tissue-confirmed glioblastoma to identify inflammatory phenotypes and develop predictive models for overall survival and personalized risk stratification. Functional principal component analysis of neutrophil-to-lymphocyte ratio-based trajectory modeling revealed four distinct inflammatory phenotypes explaining 73.8% of the observed variance, with median survival ranging from 1,004 days (high-inflammation, unstable phenotype) to 4,735 days (low-inflammation, stable phenotype; log-rank $p<0.001$). Trajectory-based models outperformed baseline-only models for predicting overall survival (C-index 0.711 versus 0.602; 18.1% improvement), demonstrating prognostic value of longitudinal features. Machine learning approaches achieved strong discrimination for predicting mortality (Random Forest AUC=0.771), with an early warning system predicting 6-month mortality with an AUC of 0.795. Among deep learning approaches, the Transformer model achieved an AUC of 0.741, approaching the performance of the best traditional machine learning models and demonstrating the potential of attention-based architectures for survival prediction. Multi-marker analyses of additional inflammatory biomarkers identified monocyte-to-lymphocyte ratio volatility as the strongest predictor of mortality (HR=1.330). These findings suggest that longitudinal trajectories of inflammatory blood markers provide additional prognostic information beyond static measurements, identify distinct phenotypes with different outcomes, and enable the development of earlier signals of disease progression for patients with GBM.

Disclosures: S. Awasthi: None. **V. Sanker:** None. **M. Lim:** None.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.03/S4

Topic: B.10. Neuro-Oncology

Title: Exploring the risk and survival of glioblastoma patients after multiple myeloma: a population-based study

Authors: *A. K. ENNIS[1], M. MILANO[2], I. MOHIUDDIN[3], A. CHOWDHRY[3];
[1]Univ. of Central Florida Col. of Med., Orlando, FL; [2]Univ. of Rochester Med. Ctr., Rochester, NY; [3]AdventHealth, Lake Mary, FL

Abstract: Purpose/Objective(s): A history of multiple myeloma (MM) may increase the risk of subsequent glioblastoma (GBM). A potential increased risk of GBM may be attributed to carcinogenic effects of MM treatments, shared genetic factors related to both malignancies, or another mechanism. We aimed to examine if a first primary malignancy of MM affects the survival of patients diagnosed with GBM. **Materials/Methods:** Using the Surveillance, Epidemiology, and End Results (SEER) database, we calculated the hazard ratio (HR) for death after GBM diagnosis associated with prior MM (and no other prior malignancies in either cohort). We also adjusted HR based on several demographic factors as well as year of diagnosis of GBM and surgical resection of GBM. **Results:** We compared the survival of 28 patients with MM followed by a second primary GBM malignancy to 28,939 patients with GBM as a first or only primary malignancy. We found an HR of 1.56 ($p=0.0215$, 95% CI: [1.07, 2.27]), indicating a greater chance of death after GBM diagnosis in those with prior MM. Increased risk of death was also significantly associated with greater age (HR:1.03 per year, $p<0.05$, 95% CI: [1.03, 1.03]), male sex (HR: 1.03, $p<0.05$, 95% CI: [1.01, 1.06]), earlier year of diagnosis (HR: 0.98 per year, $p<0.05$, 95% CI: [0.98, 0.98]), and lack of surgical treatment for GBM (HR: 0.50, $p<0.05$, 95% CI: [0.49, 0.52]). **Conclusions:** The results of this study indicate that a prior history of MM is associated with diminished survival of individuals with GBM. One possibility is that this is due to prior systemic treatment received, which may limit future systemic therapy options. Further research into the exact mechanism of the relationship between these malignancies may help elucidate the etiology.

Disclosures: A.K. Ennis: None. **M. Milano:** None. **I. Mohiuddin:** None. **A. Chowdhry:** None.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.04/Web Only

Topic: B.10. Neuro-Oncology

Title: Primary Central Nervous System Lymphoma of Pediatric Patients: Preliminary Results of a Scoping Review

Authors: *R. GARCIA GONZALEZ[1], I. PEREZ-NERI[2], O. SANDOVAL[3], D. BRAVO[3], M. OLIVERA[5], M. GARCÍA GONZÁLEZ[4], C. TREVILLA MARTÍNEZ[6], C. NATES LÓPEZ[7];
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Abstract: Background. Primary central nervous system lymphoma (PCNSL) is defined as a non-Hodgkin lymphoma confined to the brain with no evidence of systemic disease at diagnosis. In the pediatric population is rare and challenging to diagnose. Notably, cases of Hodgkin lymphoma involving the central nervous system have been reported as PCNSL, generating diagnostic controversy. Objective. To describe the clinical and diagnostic characteristics of studies reporting Hodgkin lymphoma as PCNSL in pediatric patients. Methods. A literature search was conducted in PubMed with Medical Subject Headings (MeSH) and keywords: ("Hodgkin Disease" OR "Hodgkin lymphoma") AND ("Primary Central Nervous System Lymphoma" OR PCNSL) AND (Child OR Children OR "Preschool Child" OR "Preschool Children"). Studies including patients ≤18 years of age in whom Hodgkin lymphoma was reported as PCNSL were eligible for inclusion. Study selection was performed in two stages (title/abstract and full-text screening) through independent peer review. A narrative synthesis was subsequently conducted following PRISMA guidelines using the following variables: age, sex, anatomical location of the lesion, presence or absence of systemic disease at diagnosis, histological subtype, presence of Reed-Sternberg cells, immunophenotype, cerebrospinal fluid (CSF) cytology results, Epstein-Barr virus status, disease stage, and use of monotherapy or multimodal therapy. Results. Twenty articles were identified, of which six met the inclusion criteria, reporting a total of 20 pediatric cases. Patient age ranged from 4 to 15 years, with a male predominance (~60%). Reported lesion sites included supratentorial regions, dural/leptomeningeal involvement, and thoracic epidural masses. More than 80% of patients had concomitant systemic disease at diagnosis. Classical Hodgkin lymphoma predominated, particularly the nodular sclerosis and mixed cellularity subtypes, with consistent detection of Reed-Sternberg cells and a characteristic immunophenotypic profile (CD30+, variable CD15, weak PAX5 expression). CSF cytology was predominantly negative, and Epstein-Barr virus evaluation was inconsistently reported. Most patients were classified as stage III-IV and received multimodal treatment. Conclusions. The pediatric cases included in this review do not strictly fulfill the classical diagnostic criteria for PCNSL and are more consistent with systemic Hodgkin lymphoma with secondary CNS involvement. These findings highlight the need to standardize diagnostic criteria in pediatric populations to avoid misclassification.

Disclosures: R. Garcia Gonzalez: None. **I. Perez-Neri:** None. **O. Sandoval:** None. **D. Bravo:** None. **M. Olivera:** None. **M. García González:** None. **C. Trevilla Martínez:** None. **C. Nates López:** None.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.05/S5

Topic: B.10. Neuro-Oncology

Title: PTV Margin Reduces Leptomeningeal Disease After Neoadjuvant Gamma Knife Radiosurgery for Brain Metastases

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Abstract: Neoadjuvant stereotactic radiosurgery (SRS) before resection has emerged as an alternative to postoperative SRS for large, symptomatic brain metastases, potentially reducing leptomeningeal disease (LMD) and radiation necrosis (RN). However, whether planning target volume (PTV) margin width modifies these outcomes remains unclear. We retrospectively analyzed 138 patients with 147 large symptomatic brain metastases treated with single-fraction neoadjuvant Gamma Knife radiosurgery followed by planned resection at a single institution from 2016 to 2024. The PTV-GTV margin was prespecified as the primary exposure and dichotomized at the cohort mean of 1.19 mm. Death was treated as a competing event for local recurrence, LMD, and RN using Fine and Gray regression, and propensity score matching was performed as a sensitivity analysis. The mean tumor volume was 24.6 cc, mean marginal dose was 18.5 Gy, and gross total resection was achieved in 88% of lesions. The 1- and 2-year cumulative incidences were 11.8% and 13.5% for local recurrence, 7.7% and 9.2% for LMD, and 3.9% and 6.6% for RN, respectively. Wider PTV-GTV margin was associated with a significantly lower risk of LMD (adjusted hazard ratio 0.12, 95% confidence interval 0.02-0.93, p=0.04) without a corresponding increase in RN (hazard ratio 0.66, p=0.62). In the propensity-matched cohort (51 matched pairs), the protective association persisted: 2-year LMD incidence was 15.0% in the narrower-margin group versus 3.0% in the wider-margin group (Gray's p=0.03), whereas RN remained similar (5.6% vs. 2.9%, p=0.51). Melanoma histology was independently associated with increased LMD risk. These findings suggest that, in neoadjuvant Gamma Knife radiosurgery for large brain metastases, a consistent and generous PTV margin may reduce leptomeningeal dissemination without increasing radionecrotic toxicity, likely because the high-dose irradiated tumor interface is surgically removed shortly after treatment.

Disclosures: J. Yu: None.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.06/S6

Topic: B.10. Neuro-Oncology

Support: NIH Grant R01AI158694
NIH Grant R21CA292148
American Legion Auxiliary Fellowship in Cancer Research

Title: Chronotherapy strategies for improved temozolomide efficacy in glioma

Authors: *P. A. BENDER[1], K. ECKEL-MAHAN[2];
[1]The Univ. of Texas MD Anderson Cancer Ctr. UTHealth Houston Grad. Sch. of Biomed. Sci., Houston, TX; [2]UTHealth Houston, Houston, TX

Abstract: Gliomas are common and lethal brain tumors, with high-grade variants exhibiting aggressive growth and therapeutic resistance. Standard treatment with surgery, radiation, and temozolomide (TMZ) chemotherapy offers limited survival benefits. Given the limited success of current treatments, chronotherapy, which aligns treatment with the body's natural 24-hour cycles (i.e., circadian rhythms), presents a promising approach to enhance drug efficacy. The molecular circadian clock, maintained by the transcription factors BMAL1 and CLOCK, regulates key cellular processes, including DNA repair and apoptosis. The flavonoid nobiletin (NOB), found in citrus peels, enhances circadian rhythms by upregulating BMAL1 expression and has been shown by our lab to demonstrate anti-cancer effects in hepatocellular carcinoma and acute myeloid leukemia. As similar chronotherapy approaches for glioma have not been performed, studies are underway to understand the circadian clock in glioma progression and the potential for chronotherapy and combination treatment with TMZ and NOB.
The expression of BMAL1 and CLOCK was compared across several murine and patient-derived glioma cell lines. These analyses revealed variability in BMAL1 and CLOCK expression, suggesting that tumors may differ in the robustness of their intrinsic circadian clocks. To determine whether these differences correspond to functional circadian activity, murine and patient-derived glioma cells were synchronized using serum shock to examine baseline rhythmicity. Consistent with the gene and protein expression data, glioma cells showed variable circadian clock gene rhythmicity, with some lines displaying intact molecular rhythms while others exhibited disrupted rhythmicity. Overexpression of BMAL1 and CLOCK altered the expression of additional circadian and tumor-related genes. In studies evaluating chronotherapy and the chronomodulator NOB, combination treatment reduced glioma cell viability more effectively than either treatment alone, with time-dependent changes in treatment efficacy observed. Single and combination treatments also differentially modulated circadian and tumor-related gene and protein expression and rhythmicity. Together, these findings suggest that circadian disruption may contribute to glioma progression and that targeting circadian pathways could enhance the efficacy of chemotherapy. Ongoing studies are expanding this work to in vivo models to determine how NOB and timed TMZ influence circadian gene activity and tumor progression. Ultimately, this research may help establish circadian-based therapies that improve outcomes for glioma patients.

Disclosures: P.A. Bender: None. **K. Eckel-Mahan:** None.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.07/S7

Topic: B.10. Neuro-Oncology

Support: CBF2023-2024-3425

Title: Evaluation of Carbon Nanosponges as Dual-Drug Delivery Vehicles for Chemotherapeutic Treatment of Brain Tumors

Authors: *A. SALAZAR[1], B. PINEDA OLVERA[2], V. PEREZ DE LA CRUZ[3];
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Abstract: Malignant gliomas remain highly lethal central nervous system tumors, in part because of their diffuse infiltration, marked cellular heterogeneity, and limited response to conventional chemotherapy. Drug-delivery strategies capable of improving local availability and combined antitumor activity are therefore relevant for the development of new therapeutic approaches. We evaluated carbon nanosponges as a potential dual-delivery platform for carmustine (BCNU) and quinacrine, two compounds with complementary antitumor potential in glioma models. As an initial step, UV-Vis spectrophotometric conditions were standardized to quantify both drugs and support subsequent loading and release studies. Calibration curves showed strong linearity for quinacrine and BCNU, indicating that this method can be used for reliable analytical monitoring of drug concentration. In parallel, the biological activity of each compound was characterized in malignant glioma cell lines using MTT-based viability assays. C6, RG2, and U87 cells were exposed to concentration gradients of quinacrine or BCNU for 24, 48, and 72 h to define time- and dose-dependent cytotoxic profiles. Quinacrine reduced cell viability in RG2 and C6 cultures, while BCNU and the combination of both, produced robust cytotoxic effects across the evaluated glioma models. The decrease in viability was generally concentration-dependent and became more evident over time. Together, the results establish a preclinical framework for testing carbon nanosponges as carriers for dual chemotherapeutic delivery and for comparing free-drug exposure with nanosponge-based formulations. This approach may contribute to the development of nanostructured strategies aimed at improving drug delivery, enhancing cytotoxic activity, and addressing therapeutic resistance in malignant brain tumors.

Disclosures: A. Salazar: None. **B. Pineda olvera:** None. **V. Perez De La Cruz:** None.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.08/S8

Topic: B.10. Neuro-Oncology

Title: Understanding the Effects of BIA on Blood-Brain Barrier Penetration in Pediatric Glioma Models

Authors: *T. ADEWUMI[1], J. CLARK[1], N. ANAND[2], P. VAUGHN-BEAUCAIRE[3], S. LAWLER[4];
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Abstract: Pediatric high grade gliomas(pHGG)are aggressive childhood brain tumors with no effective treatments and a median survival rate of just10 months. These tumors extensively invade normal brain tissue making them impossible to remove surgically. The major hurdle in effective drug administration for pHGG is the impenetrability of the blood-brain barrier(BBB)which protects the brain from most therapeutic agents. We previously showed that Bio-acetoxime (BIA), a derivative of the traditional Chinese medicine Indirubin, can cross the BBB and also has antimigratory effects in glioma cells. In this study we evaluated the effects of BIA on pediatric glioma cells using viability assays and flow cytometry to determine the effects of BIA onDIPG36 and SF8628 pHGG cell lines *in vitro.* We also measured effects on barrier function using an invitro3D BBB model (BBB spheroids).BIA reduced viability in both DIPG36 and SF8628 cells (IC50= 1.2 μM DIPG36 and 1.8 μM SF8628). Additionally, BIA significantly reduced cell cycle progression and this was associated with arrest inG2/M. BIA treatment was also associated with disruption of endothelial barrier integrity by In BBB spheroids we observed increased uptake of fluorescently labelled dextran indicating that BIA disrupts barrier integrity after 24 hour drug treatment. BIA treatment also reduced endothelial barrier integrity as measured by a decreased transendothelial electrical resistance (TEER).These data show that BIA may be a promising approach for the treatment of pHGG. Multiple cancer hallmarks (invasion and proliferation)are directly affected by BIA and the fact that it can enter the brain suggests it could reach these invasive cancer cells in the native space. Furthermore, the potential of BIA to disrupt endothelial cell tight junctions could improve the uptake of other drugs that could not normally enter that brain. This would potentially improve outcomes in pHGG,. In future experiments we will develop an *in vivo* mouse model to investigate the translational potential of this approach.

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Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.09/T1

Topic: B.10. Neuro-Oncology

Support: Endeavor Health SAG Pilot Grant

Title: Trans-Tumoral Current Conduction as a Potential Treatment Modality for Glioblastoma

Authors: *C. KESSINGER[1], K. ESTRADA[4], J. M. LEE[2], D. P. AKSENOV[3], J. MCDAID[1]; [1]Neurosurg., [2]Pathology, [3]Anesthesiol., Endeavor Hlth., Evanston, IL; [4]Endeavor Hlth. Ctr. for Basic Magnetic Resonance Res., Gurnee, IL.

Abstract: Glioblastoma (GBM) is a highly aggressive and treatment-resistant primary brain tumor with a poor overall prognosis. At the time of diagnosis, tumors are often large and infiltrative, making surgical resection necessary but rarely curative. Even after surgery, residual tumor cells almost inevitably remain and contribute to rapid recurrence. Postoperative treatment is further complicated by the blood-brain barrier (BBB), which severely restricts the delivery of most chemotherapeutic agents to the brain. Large or hydrophilic molecules are largely excluded, while many small lipophilic drugs that can cross the BBB are actively transported back into the bloodstream by efflux pumps such as P-glycoprotein, significantly limiting therapeutic efficacy. Residual tumor tissue that remains after resection may be inaccessible to additional surgery or systemic chemotherapy, but it may remain susceptible to electrical modulation. Electrical fields have been shown to disrupt tumor cell proliferation and viability, and tumor treating fields (TTFs) have demonstrated modest clinical benefit in GBM patients, though their efficacy may be limited by attenuation of electrical currents by the skull and surrounding tissues. To address these limitations, we propose a novel approach termed trans-tumoral current conduction (TTCC). This strategy involves implantation of a high-conductivity intra-tumoral electrode in a rat GBM model, designed to passively conduct endogenous electrical currents from surrounding healthy brain tissue, directly through the tumor mass. By bypassing both the BBB and skull impedance, TTCC may provide continuous, localized anti-tumor effects. We hypothesize that this minimally invasive, chronic intervention could suppress tumor growth and reduce recurrence after resection surgery, potentially offering an alternative or adjunct to conventional tumor resection and chemotherapy.

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Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.10/Web Only

Topic: B.10. Neuro-Oncology

Support: SECIHTI, CBF-2025-I-3231

Title: Cytotoxic effect of caffeine combinations with albendazole and albendazole sulfoxide on C6 cells

Authors: *M. HERNÁNDEZ-CERÓN[1], A. ZAFRA[4], A. DIAZ-RUIZ[5], J. FRANCO-PEREZ[2], P. BALLESTEROS-ZEBADUA[6], A. CALDERÓN-GARCIDUEÑAS[3];
[1]Neuroquímica, Inst. Nacional de Neurología y Neurocirugía, Mexico, Mexico; [2]Lab. de Patología Vascular Cerebral,, Inst. Nacional de Neurología y Neurocirugía, CDMX, Mexico;

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Abstract: Glioblastoma (GB) is the most aggressive primary brain tumor, characterized by poor prognosis and limited response to current therapies. Among the mechanisms associated with treatment failure, drug resistance mediated by transporters such as breast cancer resistance protein (BCRP) has been proposed as one of the key factors. Albendazole (ALB), an antiparasitic drug used for neurocysticercosis, is metabolized to albendazole sulfoxide (SOALB), its active metabolite, which can be transported by BCRP. In addition, ALB has demonstrated antitumor activity in several malignancies, including GB. Caffeine (CF), commonly used as a wakefulness-promoting agent, has also exhibited anticancer properties. In placental choriocarcinoma and breast cancer models, CF reduced BCRP expression and sensitized mitoxantrone-resistant cells, decreasing their IC_{50}. Objective: To evaluate the cytotoxic effects of CF combined with ALB or SOALB in glioma cells. Methods: C6 glioma cells were exposed for 72 h to ALB (0.16-1.25 μM), SOALB (2-64 μM), and CF (0.3125-10 mM). Median-effect doses (Dm) were determined by Chou et al. (2006) method, MTT viability assay and CompuSyn software. Based on Dm values, fixed-ratio combinations of ALB+CF and SOALB+CF were evaluated for synergistic, additive, or antagonistic interactions. DMSO (0.3%) and TMZ (100 μM) were used as vehicle and positive control, respectively. Morphological changes were assessed by bright-field microscopy (20× objective). Results: CF with ALB or SOALB combinations produced concentration-dependent cytotoxicity, with Dm values of 0.5 μM, 24 μM, and 1.5 mM, respectively. The highest concentration combinations exhibited synergistic cytotoxic effects. In addition, treated cells displayed morphological alterations consistent with cellular damage (figure 1). Conclusions: CF combined with ALB or SOALB may represent a promising adjuvant strategy for GB treatment due to its synergistic activity, low cost, and relatively low toxicity. Further studies in additional rodent and human glioma cell lines are needed to validate these findings.

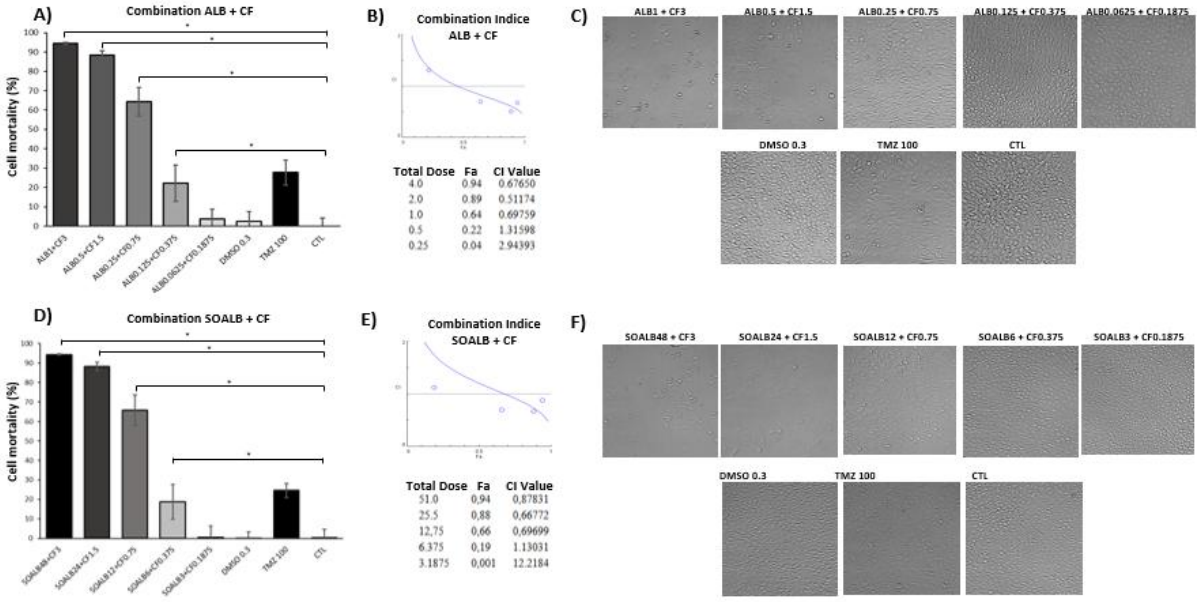


Figure 1. In vitro cytotoxicity assessment. Bars graphics of the mortality percentages for the ALB+CF (A) and SOALB+CF (D) combinations. Combination index graphics for ALB + CF (B) and SOALB + CF (E). Photomicrographs of the ALB + CF (C) and SOALB + CF (F) combinations. Data are expressed as mean ± standard deviation. N = 3 experiments with 6 replicates each. Two-way ANOVA followed by Tukey's test. * $p < 0.05$. DMSO = Dimethyl sulfoxide; TMZ = Temozolomide.

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Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.11/T2

Topic: B.10. Neuro-Oncology

Title: Antineoplastic effect of biological extracts of curcuma longa on glioblastoma cell lines

Authors: *C. RODRÍGUEZ-PÉREZ[1], V. CAMPOS-PEÑA[3], M. TORRES[2];
[1]Natl. Inst. of Neurol. and Neurosurg., Mexico city, Mexico; [2]Natl. Inst. of Neurol. and Neurosurg., Mexico City, Mexico; [3]INSTITUTO NACIONAL DE Neurología Y Neurocirugía, MEXICO CITY, Mexico

Abstract: The rhizome of *curcuma longa* contains curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), which has anti-inflammatory properties and has also been found to be highly lipophilic and capable of crossing the blood-brain barrier. Glioblastoma is the most common malignant brain tumor in adults and is considered one of the most lethal cancers. Due to its high cellular heterogeneity, it is difficult to treat. The standard treatment for

this tumor, to date, is surgical resection followed by chemotherapy and radiation. The study of the effects of curcuminoid phytochemicals with anticancer properties on glioblastoma is important for the development of alternative therapies. The aim of this study was to evaluate the antineoplastic effects of biological extracts of *curcuma longa* on glioblastoma cell lines U251, U87, F98, and C6. Biological extracts of *curcuma longa* were obtained using water and ethanol and applied in glioblastoma cell lines in cultures. Cell proliferation and migration were determined using the MTT method and bright-field microscopy in presence of extracts obtained at different time points (24 and 48 h). A dose-dependent decrease in cell proliferation and migration was observed in the different glioblastoma cell lines when using the ethanolic extracts of *curcuma longa*. These results demonstrate the therapeutic potential of downregulating oncogene pathways in glioblastoma cancer.

Disclosures: C. Rodríguez-Pérez: None. **V. Campos-Peña:** None. **M. Torres:** None.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.12/T3

Topic: B.10. Neuro-Oncology

Support: NIH 1R35GM156968

Title: Engineering a Bioluminescent Sensor for Cell Cycle Detection and Control

Authors: *A. N. KORNILOV[1], M. CHATTERTON[2], O. DUBEY[3], E. D. PETERSEN[4]; [1]Neurosci., [2]Central Michigan Univ., Mount Pleasant, MI; [3]Central Michigan Univ., Mount Pleasant, India; [4]Col. of Med., Central Michigan Univ., Mt Pleasant, MI

Abstract: The Retinoblastoma protein (pRB) is a master regulator of the G1/S phase transition of the cell cycle. pRB triggers S-phase entry upon phosphorylation by Cyclin-Dependent Kinases (CDKs) 2, 4, and 6, thus making it a critical component of neurodegenerative disease and cancer biology. In the central nervous system, pRB maintains post-mitotic neurons in a quiescent G0 state; however, pathological cell cycle re-entry driven by aberrant phosphorylation of pRB by CDKs is a known hallmark of neurodegenerative diseases like Alzheimer's as well as uncontrolled cell proliferation in brain tumors like glioblastoma. Current methods for quantifying pRB phosphorylation for cell cycle-related research typically require lysing cell samples, which precludes real-time longitudinal studies.To overcome the limitations of current methods for assessing pRB phosphorylation, we developed a novel Bioluminescent Kinase Sensor (BlinKS) to quantify RB phosphorylation state in real time. The BlinKS design utilizes a split-luciferase system, a pRB-derived phosphorylation-substrate sequence, and a phospho-amino acid-binding domain (PAABD). Phosphorylation of the pRB substrate results in its binding to PAABD, bringing together and reconstituting the split luciferase halves, allowing the enzymatic reaction of the luciferase to produce bioluminescent light.Preliminary *in vitro* testing has shown the

sensor to be functional; treatment with CDK inhibitors resulted in decreased bioluminescence compared to untreated controls that were actively dividing. Further optimization efforts of the initial successful variants, including with computational and AI-guided design tools, are underway to improve the sensors' signal-to-noise ratio and total bioluminescence output. The final version of this sensor will provide a tool for tracking the cell cycle in real time in live cells, investigating the activity of kinases upstream of pRB, as well as drug screening of potential inhibitors of upstream kinases of pRB. Ultimately, the BlinKS-RB can be paired with optogenetically-activated transcription of target genes like p53, to selectively suppress the cell cycle in cells with unwanted hyperphosphorylation of pRB, thus paving the way for potential use as a therapeutic tool.

Disclosures: A.N. Kornilov: None. **M. Chatterton:** None. **O. Dubey:** None. **E.D. Petersen:** None.

Poster

PSTR347: Neuro-Oncology: Therapeutics, Diagnostics, and Clinical Outcomes

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.13/T4

Topic: B.10. Neuro-Oncology

Title: Molecular mechanisms and clinical implications of glioma: current perspectives

Authors: Y. AN[1], S. CHOI[1], S. JUN[1], H. KANG[1], S. KIM[1], Y. SEO[1], E. SHIM[1], ***S. CHOI**[2]; [1]Dept. of Med. Sci., Col. of Medicine, Catholic Kwandong Univ., Gangneung, Korea, Republic of; [2]Dept. of Pharmacol., Catholic Kwandong Univ., Gangneung-si, Korea, Republic of

Abstract: Glioma is a representative primary brain tumor originating from glial cells or precursor cells in the central nervous system. Depending on the location, size, and growth rate of the tumor, it causes various neurological symptoms such as headaches, seizures, motor paralysis, and cognitive decline. In particular, complete surgical removal is nearly impossible due to its highly invasive growth characteristic, where tumor cells irregularly invade the boundaries of normal brain tissue. Consequently, high-grade tumors such as glioblastoma, which account for more than half of malignant primary brain tumors, exhibit high recurrence rates and treatment resistance, remaining an unresolved clinical challenge in oncology. In the past, diagnosis heavily relied on microscopic histological findings; however, it has recently been revealed that the molecular genetic characteristics of the tumor play a crucial role in diagnosis, prognosis prediction, and treatment response evaluation. Following the revision of the 2021 WHO Classification of Tumors of the Central Nervous System (WHO CNS5) guidelines, the diagnostic criteria have completely shifted from conventional morphological findings to an 'Integrated Diagnosis' system that mandatorily reflects molecular markers such as isocitrate dehydrogenase (IDH) mutation, 1p/19q codeletion, O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and epidermal growth factor receptor (EGFR) amplification. We aim to review the core molecular biological mechanisms involved in the development and tumor

evolution of glioma. Furthermore, we will analyze the principles of molecular marker-based integrated diagnosis according to the latest WHO CNS5 classification system and how this overcomes the limitations of current clinical practices.

Disclosures: Y. An: None. **S. Choi:** None. **S. Jun:** None. **H. Kang:** None. **S. Kim:** None. **Y. Seo:** None. **E. Shim:** None. **S. Choi:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.01/T5

Topic: C.01. Brain Wellness and Aging

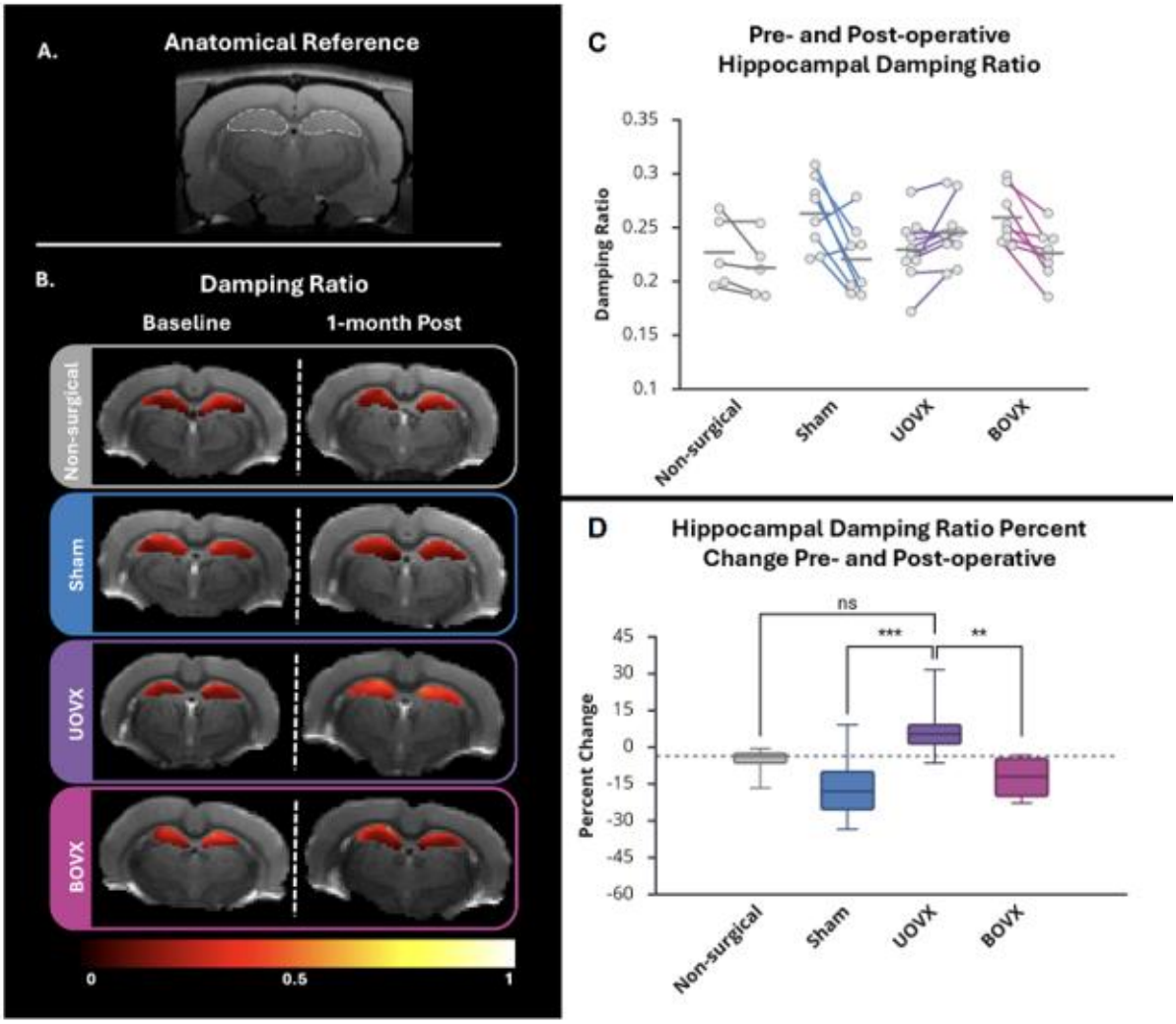
Support: NIBIB R01 EB027577
NIGMS 2P20 GM103650
NIGMS U54-GM104941
NIGMS P20 GM103446

Title: Magnetic Resonance Elastography Reveals Estrogen-Related Changes to Hippocampal Tissue Viscoelasticity in Rat Models of Perimenopause and Menopause

Authors: *S. VANDER WIELE[1], K. MILBOCKER[1], K. PENNA[2], M. BISCHOFF[3], A. Y. KLINTSOVA[3], C. JOHNSON[4];
[1]Biomed. Engin., [2]Biol. Sci., [3]Psychological and Brain Sci., [4]Univ. of Delaware, Newark, DE

Abstract: Hormone-driven mechanical changes to peripheral tissues are well-documented in menopause (e.g. cervical tissue stiffening); however, the impact of estrogen fluctuations on brain tissue mechanics remains unknown. Estrogen regulates brain microstructure through effects on myelination, glial activity, and extracellular matrix remodeling that contribute to overall tissue viscoelasticity. We sought to assess the effect of menopause on brain tissue mechanics via magnetic resonance elastography (MRE)—a noninvasive MRI technique that uses vibrations to quantify tissue stiffness and damping ratio (relative viscosity). Previous work showed that low-estrogen phases of the rat estrous cycle were associated with increased hippocampal damping ratio in young adulthood. We further investigated whether partial or total depletion of circulating estrogen in aged rats modeling perimenopause and menopause led to similar changes in the hippocampus. Female Sprague Dawley rats in estropause underwent unilateral ovariectomy (UOVX; n=10), bilateral ovariectomy (BOVX; n=8), or sham surgery (n=8). MRE and anatomical scans were performed pre-OVX and one-month post-OVX using a 9.4T Bruker MRI. Mechanical property maps were estimated across the whole brain using tissue displacement data and a nonlinear inversion algorithm. A one-way ANOVA revealed a significant effect of surgical condition on dorsal hippocampal damping ratio ($p<0.001$, $\eta^2=0.46$). UOVX rats showed an average of 23% increase in hippocampal damping ratio relative to sham controls ($p<0.001$), while BOVX rats exhibited a non-significant relative 4.9% increase ($p=0.957$, Fig. 1). MRE

detected menopause-associated changes in hippocampal tissue mechanics, with distinct viscoelastic alterations in UOVX animals modeling perimenopause. These findings suggest that brain mechanical alterations are greatest during the perimenopausal hormonal transition and may reach a new homeostatic equilibrium following complete estrogen depletion, highlighting MRE's potential as a biomarker of hormone-related brain remodeling.



Disclosures: S. Vander Wiele: None. **K. Milbocker:** None. **K. Penna:** None. **M. Bischoff:** None. **A.Y. Klintsova:** None. **C. Johnson:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.02/T6

Topic: C.01. Brain Wellness and Aging

Support: Estonian Research Council Grant PRG2544
Estonian Research Council Grant PRG685

Title: Alterations in the kynurenine metabolic pathway in patients with schizophrenia spectrum disorders and in a mouse model with Negr1 deficiency

Authors: *C. KUUSKMAE[1], M.-A. PHILIPS[1], L. HARING[2], E. VASAR[1];
[1]Dept. of Physiol., [2]Dept. of Psychiatry, Univ. of Tartu, Tartu, Estonia

Abstract: Psychosis in schizophrenia spectrum disorders (SSD) involves immune-metabolic and glutamatergic disturbances, yet their molecular signatures and kynurenine pathway component remain unclear. This exploratory translational study centred on a new multi-omic analysis of antipsychotic-naive first episode psychosis (FEP), with longitudinal clinical and brain-level mouse data.

In a cohort of 66 FEP patients and 51 matched controls, serum targeted liquid chromatography-mass spectrometry metabolomics and plasma Olink proteomics were integrated after quality control. After false-discovery-rate correction, 90 features differed between groups. Elastic net logistic regression across 50 stratified train-test splits achieved a mean area under the curve of 0.95 and yielded a 19-feature immuno-metabolic panel. The panel combined inflammatory proteins, lipids, and metabolites. Anthranilic acid and kynurenic acid (KYNA) were selected in 90% and 78% of iterations, respectively. Both were lower in patients and contributed toward control classification, linking the kynurenine pathway to the FEP signature.

Longitudinal serum mass spectrometry in an overlapping cohort (54 SSD patients, 58 controls) clarified temporal context. Before treatment, tryptophan, kynurenine, KYNA, and anthranilic acid were reduced. After 0.6 years of antipsychotic treatment, most differences attenuated, while tryptophan and 3-hydroxykynurenine remained significantly reduced. At 5.1 years, kynurenine pathway differences were modest, but the xanthurenic acid/KYNA ratio shifted toward xanthurenic acid. Changes in the kynurenine pathway were associated with metabolic syndrome.

To investigate brain biochemistry during controlled pharmacological challenge and behavior, and assess plasma-brain correspondence, kynurenine metabolites were measured in plasma and four brain regions of male and female neuronal growth regulator 1 (*Negr1*)-deficient and wild-type mice (12-14 per metabolite group), alongside locomotor responses to the N-methyl-D-aspartate receptor antagonist dizocilpine (MK-801). Mutant males showed increased acute MK-801-induced locomotion. Frontal-cortical xanthurenic acid and glutamate increased in mutant males but decreased in mutant females. Quinolinic acid also decreased in mutant females. Results in plasma and brain varied by sex and genotype rather than showing uniform correspondence.

Thus, multi-omic findings position anthranilic acid and KYNA within an immuno-metabolic signature of untreated FEP, while longitudinal and mouse data show that kynurenine alterations depend on illness stage, metabolic state, sex, genotype and tissue.

Disclosures: C. Kuuskmae: None. **M. Philips:** None. **L. Haring:** None. **E. Vasar:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

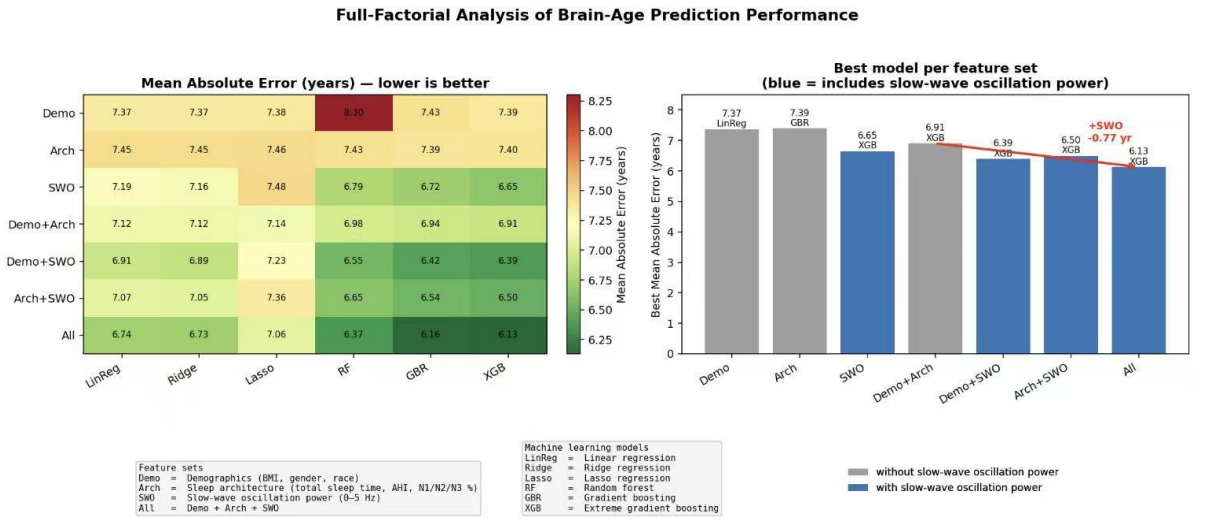
Program #/Poster #: PSTR348.03/T7

Topic: C.01. Brain Wellness and Aging

Title: Quantifying the Predictivity of Slow-Wave Activity during Non-Rapid Eye Movement Sleep in Brain Age Inference

Authors: *O. ZHU[1], F. LIU[2];
[1]The Harker Sch., Santa Clara, CA; [2]Stevens Inst. of Technol., Hoboken, NJ

Abstract: While sleep slow-wave activity is known to decline with age and may provide a neurophysiological marker of brain aging, the extent to which it contributes to brain-age predictions has not been fully explored. This study examines the contribution of slow-wave oscillation (SWO) power during sleep using a full-factorial comparison of feature sets and machine-learning models based on the Sleep Heart Health Study (SHHS) dataset (n = 7,312). Three groups of features were created: demographics, sleep architecture metrics, and SWO power. The demographics group contains bmi, gender, and race. The sleep architecture group contains metrics such as total sleeping time, Apnea-Hypopnea Index (AHI), and the distribution of the total sleep time across N1, N2, and N3. YASA sleep staging was used to determine the stages. The third group contains SWO power with a frequency range of 0 to 5 Hz that was calculated through DYNAM-O's program, which uses the multitaper algorithm. From these 3 groups, 7 different feature sets and 6 different machine learning algorithms were used, forming 42 total combinations. The algorithms were Linear Regression, Ridge Regression, LASSO Regression, Random Forest, Gradient Boosting Regression, and Extreme Gradient Boosting. Performance was assessed using mean absolute error (MAE). Models incorporating SWO power consistently outperformed corresponding models without SWO power. Using the Extreme Gradient Boosting method on all three groups was the most effective and had a MAE of 6.13. These findings suggest that SWO power can serve as a valuable EEG biomarker of brain aging and improve the accuracy of brain age predictions.



Disclosures: O. Zhu: None. **F. Liu:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.04/T8

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIA R01 AG053555

Title: Distinct Perilesional Cerebrovascular Reactivity Gradients Around Periventricular and Deep White Matter Hyperintensities in Cognitively Unimpaired Older Adults

Authors: *Y. ZHAO[1], D. PARKER[3], J. N. ADAMS[5], S. KIM[3], S. SIMMONS[4], J. R. BOCK[2], L. MCMILLAN[5], M. A. YASSA[4];
[2]Neurobio. and Behavior, [1]Univ. of California, Irvine, Irvine, CA; [4]Neurobio. and Behavior, [3]Univ. of California Irvine, Irvine, CA; [5]Neurobio. and Behavior, UC Irvine, Irvine, CA

Abstract: White matter hyperintensities (WMHs) are commonly observed in aging and preclinical Alzheimer's disease (AD), yet it remains unclear whether vascular alterations within and around WMHs reflect localized cerebrovascular impairment or spatially extended perilesional physiology. The current study examined whether resting-state BOLD-derived cerebrovascular reactivity (CVR) varies with distance from WMHs and by WMH subtype. Participants included 78 older adults from the Biomarker Exploration of Aging, Cognition, and Neurodegeneration (BEACoN) preclinical AD study (age: 70.3 ± 7.2 years; 26 female). WMHs were segmented from FLAIR using ANTsXNet with manual correction, and were classified into periventricular (PV) and deep subtypes based on Euclidean distance from the lateral ventricles (≤10 mm: PV; >10 mm: deep). CVR was estimated by regressing 0.02-0.04 Hz bandpass-filtered BOLD fluctuations against a whole-brain reference signal and quantified within Euclidean distance shells from the WMH boundary (core, 0-3, 3-6, 6-9, 9-12 mm) and normal-appearing white matter (NAWM; >12 mm). Results showed that CVR was reduced relative to NAWM across all distance shells for both subtypes (FDR-corrected, all $p<0.001$), yet linear contrasts confirmed significant distance-dependent gradients for both PV and deep WMHs (PV: $t(77)=7.04$, $p<0.001$; Deep: $t(77)=6.94$, $p<0.001$). These gradients differed significantly in steepness (interaction: $t(77)=-3.20$, $p=0.002$), with deep WMHs showing a more pronounced spatial gradient. In contrast to this overall perilesional CVR reduction, PV perilesional CVR unexpectedly showed a positive association with WMH burden, with stronger associations in more distal perilesional shells (core: $r=0.28$, $p=0.013$; 3-6 mm: $r=0.42$, $p<0.001$; 6-9 mm: $r=0.52$, $p<0.001$; 9-12 mm: $r=0.63$, $p<0.001$). No comparable burden-CVR pattern was observed for deep WMHs. WMH burden-CVR associations differed significantly between PV and deep WMHs beginning at the 3-6 mm shell and extending to more distal shells (Fisher z-tests, all $p<0.01$). Elevated PV-proximal CVR (3-12 mm) was also associated with poorer temporal mnemonic discrimination ($r=-0.269$, $p=0.020$). These findings suggest biologically distinct

vascular processes surrounding PV versus deep WMHs. Specifically, higher PV perilesional CVR was associated with greater PV WMH burden and poorer temporal mnemonic discrimination, suggesting a potentially maladaptive rather than compensatory vascular response. Future work will examine associations of elevated PV perilesional CVR with fluid- and imaging-based inflammatory and AD biomarkers.

Disclosures: Y. Zhao: None. **D. Parker:** None. **J.N. Adams:** None. **S. Kim:** None. **S. simmons:** None. **J.R. Bock:** None. **L. McMillan:** None. **M.A. Yassa:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.05/T9

Topic: C.01. Brain Wellness and Aging

Support: NIH CrossROADS T32

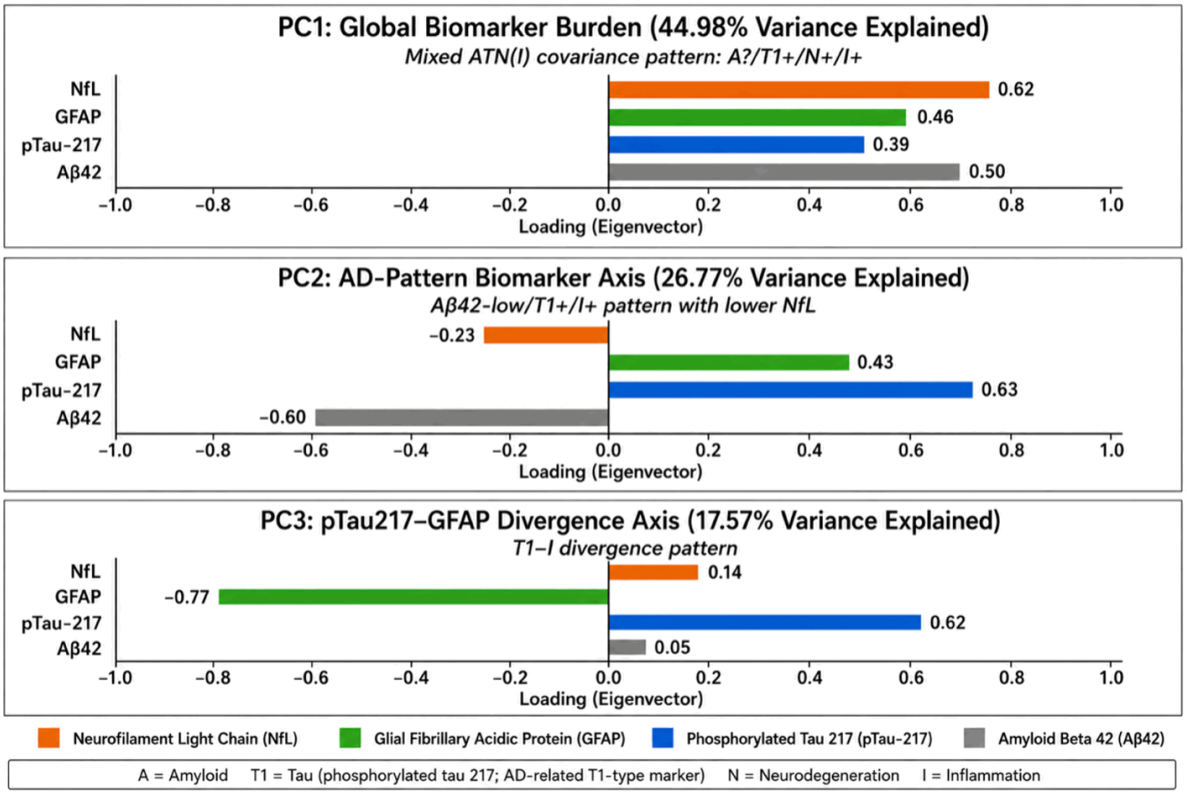
Title: Composite Plasma Biomarker Risk Phenotypes and Brain Age Gap Reveal Cognitive Resilience Among Cognitively Unimpaired Oldest-Old

Authors: *K. H. JOHNSON[1], S. MERRITT[2], T. RUNDEK[2], B. ASKEN[3], K. M. VISSCHER[5], H. GARDENER[2], G. ALEXANDER[6], R. COHEN[3], E. C. PORGES[3], K. MCGREGOR[7], V. A. DEL BENE[8,9], M. K. BRITTON[4], J. P. DE RIVERO VACCARI[10];
[2]Neurol., [1]Univ. of Miami Miller Sch. of Med., Miami, FL; [3]Clin. and Hlth. Psychology, [4]Dept. of Epidemiology, Col. of Med. and Col. of Publ. Hlth. and Hlth. Professions, Univ. of Florida, Gainesville, FL; [5]Neurobio., Univ. of Alabama at Birmigham, Birmingham, AL; [6]Univ. of Arizona, Tucson, AZ; [7]Clin. and Diagnos. Sci., [8]Heersink Sch. of Med., [9]Heersink Sch. of Medicine, Dept. of Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [10]Neurolog. Surgery, Univ. of Miami, Miami, FL

Abstract: Background: Some adults aged ≥85 years maintain preserved cognition despite biological risk factors for neurodegeneration. We examined whether plasma biomarkers of Alzheimer's disease (AD)-related pathology identify biologically vulnerable subgroups within a cognitively unimpaired oldest-old cohort and whether these phenotypes are associated with structural brain aging. **Methods:** We analyzed 159 cognitively unimpaired adults aged ≥85 years from the McKnight Brain Aging Registry. Plasma pTau217, Aβ42, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) were measured using the Simoa platform, and thresholds from prior studies were used to identify elevated neurodegenerative risk. Principal component analysis (PCA) identified latent biomarker phenotypes based on covariance patterns, with participants assigned according to their dominant component. Brain age gap (BAG) was calculated as MRI-predicted brain age minus chronological age; BAG≤0 indicated favorable brain aging. **Results:** Participants had a mean (SD) age of 88.4 (+/-3.2) years, 53% were women, 58% had hypertension, 45% hypercholesterolemia, and 9% diabetes. Elevated biomarker burden

was common: 53% had pTau217 > 0.55 pg/mL, 82% had NfL > 20 pg/mL, and 78% had GFAP > 100 pg/mL. The PCA identified three biological constructs **(Figure 1)** explaining 89% of biomarker variance: Global Biomarker Burden, AD-Pattern Biomarker Axis, and pTau217-GFAP Divergence Axis. Despite substantial biomarker heterogeneity, 92.5% of participants exhibited favorable BAG. Favorable BAG predominated across all biomarker phenotypes (90.9%-97.6%), with no significant association between phenotype and BAG. For individual biomarkers, higher pTau217 was associated with more negative BAG (r=-0.22, p=0.007). **Conclusions:** In cognitively unimpaired adults aged ≥85, plasma biomarkers revealed heterogeneous neurodegenerative risk, yet most showed a favorable brain age gap. This mismatch suggests resilience and supports multimodal biomarker phenotyping to identify healthy brain aging trajectories.

Figure 1: Principal Component Analysis Eigenvalues for Plasma Biomarkers in the Oldest Old (Ages ≥ 85 Years)



Disclosures: K.H. Johnson: None. **S. Merritt:** None. **T. Rundek:** None. **B. Asken:** None. **K.M. Visscher:** None. **H. Gardener:** None. **G. Alexander:** None. **R. Cohen:** None. **E.C. Porges:** None. **K. McGregor:** None. **V.A. Del Bene:** None. **M.K. Britton:** None. **J.P. De Rivero Vaccari:** A. Employment/Salary (full or part-time):; Co-founder and Managing Member of InflamaCORE, LLC. F. Consulting Fees (e.g., advisory boards); ZyVersa Therapeutics.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.06/T10

Topic: C.01. Brain Wellness and Aging

Title: Differential associations between cognitive reserve domains and neurocognitive performance in young adults

Authors: I. BAULIAH[1], P. PETHIYAGODA[1], E. FEDOROVSKAYA[1], *R. J. HOUSTON[2]; [1]Integrated Sci. Acad., [2]Rochester Inst. of Technol., Rochester, NY

Abstract: Cognitive reserve (CR) is thought to reflect a person's resilience against cognitive decline, particularly in the face of brain injury and neurodegenerative diseases. As a result, CR may serve as biomarker for brain wellness and recovery outcomes. While some studies utilize proxy measures of CR such as education level or IQ, the Cognitive Reserve Index questionnaire (CRIq) comprehensively quantifies CR through education, job activity, and leisure activities. Multiple studies have demonstrated positive associations between CRIq scores and neurocognitive functioning, particularly in relation to memory and executive functioning. However, most of this research heavily focuses on older adults or those already with deficits (e.g., dementia, Parkinson's Disease). Little research has examined these associations in young adults, leaving the relationship between early-adulthood CR and specific cognitive phenotypes poorly understood. A preliminary sample of young adults (N=14; *M* age= 19.64 years; 6 men, 6 women, 1 non-binary, and 1 bigender) were recruited through a university participant pool to complete a screening survey including a self-report version of the CRIq and an in-person neuropsychological assessment of memory and executive functioning. Correlations were conducted between CRIq scores (Education, Working Activity, Leisure Activity) and neuropsychological performance. Analyses indicated positive relationships between cognitive reserve and verbal memory performance. Specifically, CRIq Working Activity scores were correlated with measures involving semantic memory such as WMS Logical Memory (*r*'s =.52 to .69) and CVLT recall performance (*r*'s =.48 to .66). Alternatively, CRIq Education scores were related to associative memory tests such as the WMS Visual Paired Associates subtest (*r*'s =.42 to .67). CRIq Leisure Activity scores were correlated with non-verbal memory performance on the Rey Complex Figure Short and Long Delay recall (*r*'s =.65). Working memory, as indicated by Digit Span Backwards performance, was positively correlated with CRIq Working and Leisure Activity scores (*r*'s =.36 to .53). In terms of executive functioning, verbal fluency performance was correlated with CRIq Working Activity (*r*'s =.36 to .59) although CRIq scores were not related to cognitive flexibility as indicated by Trail Making B performance. These findings extend prior work to a young adult sample, but also suggest differential associations with specific facets of cognitive reserve and neurocognition. Although preliminary, results suggest important points for future research and intervention efforts to mitigate risk for cognitive decline.

Disclosures: I. Bauliah: None. **P. Pethiyagoda:** None. **E. Fedorovskaya:** None. **R.J. Houston:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.07/T11

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant 1R01AG064010-01

Title: Longitudinal impacts of baseline global cognition on cerebellar network connectivity and behavioral performance

Authors: *B. M. LOWE, J. A. BERNARD;
Psychological and Brain Sci., Texas A&M Univ., College Station, TX

Abstract: Background: The cerebellum has been recognized for its role beyond motor control and planning, influencing a wide range of cognitive functions and contributing to cerebral network connectivity. Because this structure undergoes age-related structural and network changes, it makes investigations of the cerebellum and associated variables of influence on performance in advanced age an area of interest. Here, we examined longitudinal differences in resting-state connectivity based on baseline global cognitive status, and relationships with behavioral performance. **Methods:** $N = 138$ human participants completed cognitive and imaging measures at three time points (baseline, 12-months, and 24-months). Cognitive status (i.e., high or low) was determined by performance on the Montreal Cognitive Assessment (MoCA). Using resting-state functional MRI (fcMRI), group baseline and longitudinal connectivity were examined for cognitive (Crus I/II) and sensorimotor (Lobules V/VI) cerebellar regions across four cognitive tasks: digit span, letter-number sequencing, symbol span, and digit-symbol coding. **Results:** Common trends were noted across group, cerebellar region, and cognitive task. We found that participants with lower cognitive status at baseline showed increased connectivity at both baseline and over a 24-month period, relative to participants with higher global cognition, implying possible engagement of compensatory mechanisms. Additionally, connectivity patterns were less robust for this group. Regionally, Crus I and II were found to have a higher degree of overall connectivity, particularly with the prefrontal cortex, relative to Lobules V and VI. These trends were evident across all four cognitive tasks. **Conclusion/Implications:** The findings shed light on how global cognitive status modulates cerebral-cortical dynamics and the extent to which future cognitive ability can be predicted. Additionally, investigations into global cognition could reveal it as a protective factor for risk and resilience against neurodegenerative diseases and mild cognitive impairment.

Disclosures: B.M. Lowe: None. **J.A. Bernard:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.08/T12

Topic: C.01. Brain Wellness and Aging

Support: CIHR Postdoctoral Fellowship MFE-201012
Wellcome Leap CARE-2025-2571407103

Title: Effects of menopause hormone therapy on cognition vary by composition and presence of genetic risk for Alzheimer's disease

Authors: *M. PEROVIC, L. A. GALEA;
Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: Implications of menopause hormone therapy (MHT) for cognitive aging remain unclear despite decades of research. Potential reasons include insufficient consideration of MHT composition, despite notable pharmacokinetic differences across formulations, and limited attention to individual differences that may exacerbate cognitive risk. We examined neurocognitive outcomes in cognitively unimpaired participants (N=8,741) and participants with mild cognitive impairment (N=5,653) as a function of APOEε4 status, the strongest genetic predictor of Alzheimer's disease, and hormonal composition of MHT. Results suggest composition- and domain-specific effects on cognition. In cognitively unimpaired participants, estradiol was associated with better episodic memory, conjugated estrogens alone with better verbal ability but worse verbal ability with the addition of medroxyprogesterone acetate. Neuroimaging analyses available for a subset of participants (N=930) revealed a consistent pattern of more favourable outcomes (higher volume, cortical thickness; less white matter damage) in APOEε4 carriers taking estradiol. Finally, survival analyses indicated that cognitively unimpaired participants taking estradiol therapy were at lower risk of progressing to mild cognitive impairment. In participants with mild cognitive impairment, APOEε4 carriers using estradiol and conjugated estrogens had better verbal performance than MHT non-users. However, performance benefits for non-carriers were only seen with estradiol use. Survival analyses found no significant effect of MHT use on risk of progression to dementia, suggesting that, in participants who are already cognitively impaired, MHT may improve functional status without ultimately preventing progression. These results underscore the importance of considering MHT composition and individual risk factors when assessing MHT effects on cognition, reframing mixed MHT findings as an issue of exposure definition and supporting composition-, genetic risk-, and cognitive status-aware approaches to menopause care.

Disclosures: M. Perovic: None. **L.A. Galea:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.09/T13

Topic: C.01. Brain Wellness and Aging

Title: Elevated Serum Neurofilament Light Chain in Canine Cognitive Dysfunction Is Independent of Peripheral Neuroinflammatory Cytokine Profiles

Authors: ***K. PARK**, S. LEE, S.-Y. NA, Y. KANG, K. RADHAKRISHNAN, P. J. SWEENEY, L. PARK;
Naason Sci., Cheongju-si, Korea, Republic of

Abstract: Canine cognitive dysfunction (CCD) is an age-related neurodegenerative disorder that shares clinical and neuropathological features with Alzheimer's disease, including amyloid-β accumulation, axonal degeneration, microglial activation, and synaptic dysfunction. Neurofilament light chain (NfL), released into circulation following neuroaxonal injury, has emerged as a sensitive blood-based biomarker of neurodegeneration in humans. Chronic systemic inflammation, reflected by cytokines such as IL-6, TNF-α, and IFN-γ, has also been implicated in cognitive decline. To evaluate the relationship between neuroaxonal injury and systemic inflammation in CCD, serum NfL was measured using Simoa technology and seven plasma cytokines (IFN-γ, TNF-α, IL-2, IL-6, IL-8, IL-10, MCP-1) were quantified in 46 client-owned dogs spanning young to very old age groups, including 16 dogs diagnosed with CCD. Serum NfL concentrations were markedly elevated in dogs with CCD (597.9 ± 225.3 pg/mL) compared with non-CCD controls (82.3 ± 24.0 pg/mL; $p < 0.001$), indicating ongoing neuroaxonal degeneration. Among control dogs, NfL increased progressively with age, supporting its utility as a biomarker of physiological brain aging. Of the cytokines with sufficient measurable values (IL-6, IL-8, MCP-1), only IL-6 was significantly increased in CCD dogs, whereas IL-8 and MCP-1 showed no group differences. Importantly, no significant correlations were observed between serum NfL and any quantified cytokine, including IL-6, indicating that neuroaxonal injury and peripheral inflammatory signaling are biologically distinct processes in CCD. These findings support serum NfL as a robust blood-based biomarker of neuroaxonal injury and brain aging in dogs with CCD. The lack of association between NfL and peripheral cytokines suggests that structural neurodegeneration and systemic immune activation represent distinct biological domains, and that progressive neuroaxonal loss in CCD may occur independently of measurable peripheral cytokine-mediated inflammation. This work establishes a translational framework for evaluating blood-based biomarkers of neurodegeneration in a spontaneous large-animal model of cognitive aging.

Disclosures: K. Park: None. **S. Lee:** None. **S. Na:** None. **Y. Kang:** None. **K. Radhakrishnan:** None. **P.J. Sweeney:** None. **L. Park:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.10/T14

Topic: C.01. Brain Wellness and Aging

Title: Altered temporal coordination of conflict-related neural processes in young adults with a family history of Alzheimer's Disease

Authors: E. LENCHENKOVA[1], C. LARGE[1], R. J. HOUSTON[2], *E. FEDOROVSKAYA[1]; [2]Psychology, [1]Rochester Inst. of Technol., Rochester, NY

Abstract: Prior research has shown altered P3 latency in healthy older adults with a family history of Alzheimer's and in APOE4 carriers (Pedoroso et al., 2021), as well as differences in P3 amplitude (Paitel & Nielson, 2024). Young adults with a family history have also shown neural differences in stop-signal and oddball paradigms (Paitel & Nielson, 2022). However, understanding of conflict processing in young adults with a family history of Alzheimer's Disease is still limited, warranting further investigation. In this exploratory study, we compared cognitive performance and ERP responses in young adults with and without a family history of Alzheimer's disease during a Stroop Task. Participants (N=39; M age = 20.6 years; 15 men/24 women) with (AD+; n=7) and without (AD-; n=32) a family history of Alzheimer's disease completed the Symbol Digit Modalities Test (SDMT) to assess processing speed as well as a Stroop Task during which EEG was recorded. SDMT results suggest a trend of slower processing in the AD+ group (M = 56.0, SD = 6.8) compared to the AD- group (M = 59.2, SD = 10.6). Response times for the Stroop showed a significant interference effect, but no group differences. Linear mixed-effects model and post hoc comparisons suggest differences in neural response patterns between the groups, driven by differences in N2 amplitude and P3 latency patterns. Overall group variance was significant across early N2 and late P3 components (p's < .025). Post-hoc Welch's t-tests showed that the AD+ group exhibited a significantly more negative N2 mean amplitude at Pz specifically during the congruent condition, $t(12.18) = -2.56$, $p = .025$. This baseline response was accompanied by an early temporal shift during the Incongruent condition: the AD+ group exhibited an accelerated N2 peak latency at Pz, $t(9.48) = -2.16$, $p = .057$). The combination of amplitude and latency differences at Pz suggests differences in the timing of conflict processing between groups. In the late executive window, individual condition contrasts revealed a trend at Pz indicating that the AD+ group exhibited longer P3 latency for congruent compared to neutral trials than the AD- group ($p=.051$). Incongruent-to-congruent trial comparison within the AD+ group at Fz revealed larger P3 amplitudes ($p=.035$). Neutral-to-high-conflict incongruent trial comparisons showed a significant processing delay ($t(74)=2.01$, $p=.049$) in this group. Although preliminary, the patterns of early temporal acceleration and late frontal-central shifts may point to an underlying conflict processing timing difference, whereby AD+ individuals alter their neural pacing and processing strategies to maintain behavioral performance.

Disclosures: E. Lenchenkova: None. **C. Large:** None. **R.J. Houston:** None. **E. Fedorovskaya:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.11/T15

Topic: C.01. Brain Wellness and Aging

Support: NMSS Pilot Research Grant

Title: Biomarkers of the resiliency to cognitive decline in multiple sclerosis

Authors: *T. J. COVEY[1], M. TRIPOLI BALKO[2], H. NYARADY[3];
[1]Univ. At Buffalo, Buffalo, NY; [2]Neurosci. Program, Jacobs Sch. of Med. and Biomed. Sciences, State Univ. of New York at Buffalo, Buffalo, NY; [3]Pharmacol. and Toxicology, Univ. at Buffalo, Jacobs Sch. of Med. and Biomed. Sci., Buffalo, NY

Abstract: Multiple Sclerosis (MS) is a neurodegenerative disorder that involves multifocal lesions, white and gray matter atrophy, and brain network disruption. Cognitive deficits are commonly reported by people with MS (PwMS), and are associated with disruption to activities of daily living. However, PwMS with similar lesion load can exhibit distinct cognitive outcomes. Some individuals may experience clear cognitive disturbance, whereas other individuals with similar neuropathology may exhibit intact cognitive performance. The ability to maintain sufficient cognitive performance to perform tasks of daily living in the face of neuropathology is referred to as cognitive reserve. High cognitive reserve has been associated with proxy measures such as educational attainment and premorbid intellectual functioning. PwMS with high cognitive reserve tend to exhibit better cognitive outcomes, but the neural mechanisms underlying cognitive reserve and the resiliency to cognitive decline in MS are not well understood. We sought to identify neural underpinnings of neural compensation and the resiliency to cognitive decline in a study where we obtained event-related potentials during a clinically relevant cognitive test in PwMS and healthy controls. We developed a computerized version of the Symbol Digit Modalities Test (SDMT), which is a clinically validated neuropsychological test that is commonly used to evaluate cognitive processing speed in MS. For each trial of the computerized version of the task that we developed, participants had to determine the number that was associated with a symbol test item using a symbol-digit key at the top of the screen. Study participants that performed well on the task demonstrated pronounced posterior electrode P1, frontal N2, and posterior P3 amplitude - this neural activity profile could therefore serve as a concise biomarker of intact cognitive functioning. In addition, some participants also demonstrated a shift in ERP component measures, in which there was a reduction of central N2 with concomitant enhancement of central P3 amplitude - this neural activity profile was interpreted as a concise biomarker of neural compensation. We posit that the shift in central N2/P3 component amplitude can provide a neural index of the resiliency to cognitive decline and cognitive reserve. Furthermore, the fact that this shift occurred in the N2 and P3 components suggests that compensatory brain functioning is primarily instantiated at stages of information processing that involve cognitive control, stimulus categorization, and decision-making, likely requiring recruitment of neural resources associated with executive brain networks.

Disclosures: T.J. Covey: None. **M. Tripoli Balko:** None. **H. Nyarady:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.12/T16

Topic: C.01. Brain Wellness and Aging

Support: NIH Intramural Grant

Title: Bioenergetic reprogramming and metabolic resilience driven by mitovesicle-enriched extracellular nanoparticles confer robust neuroprotection in glaucoma: an integrated multi-omics study

Authors: *S. K. VISHWAKARMA[1], M. GEDDA[2], D. KUMAR[3], S. I. TOMAREV[3];
[1]Section of Retinal Ganglion Cell Biology, LRCMB, Natl. Eye Institute, Natl. Inst. of Hlth., Bethesda, MD; [2]NHLBI, NIH, Bethesda, MD; [3]SRGCB, LRCMB, NEI, NIH, Bethesda, MD

Abstract: Purpose Bioenergetic failure and metabolic dysfunction are key drivers of retinal ganglion cell (RGC) vulnerability in glaucoma, yet therapeutic strategies to restore these pathways remain largely unexplored. This study used integrated multi-omics profiling to determine whether mitovesicle-enriched extracellular nanoparticles (ME-ENPs) counteract glaucomatous neurodegeneration by activating coordinated bioenergetic, metabolic, and neuroprotective mechanisms. **Methods** ME-ENPs were purified from human iPSC-conditioned medium using buoyant-density ultracentrifugation and characterized. Neuroprotective effects of ME-ENPs were tested in mouse mixed retinal cultures (MRCs) and in an ocular hypertension mouse model (OHM). BRN3B-H9-derived human RGC-like cells were stressed with sodium azide (SA) and treated for 24h with crude preparation, different purified fractions, and ME-ENPs. Transcriptional and metabolic responses were mapped using integrated mRNA sequencing and untargeted metabolomics, followed by differential expression and pathway analyses. RGC bioenergetics was validated using Seahorse extracellular flux assays. **Results** High-resolution fractionation identified a distinct ME-ENP population enriched in fractions 16-20 out of 30. ME-ENPs contained a heterogeneous ensemble of exosomes, microvesicles, mitovesicles (30-200nm), and <50nm nanoparticles (exomeres and supermeres). Relative to the crude preparation and all other fractions, ME-ENPs treatment significantly increased RGC survival and axonal growth in MRCs after 72h. Intravitreal delivery of ME-ENPs in OHM mice better preserved RGCs across peripheral (>13%), mid-peripheral (>9%), central (>19%), and whole-retina (>16%) regions 60 days post-injury. Transcriptomic profiling of SA-stressed RGC-like cells after ME-ENPs treatment revealed a more robust and coordinated activation of bioenergetic, metabolic, and neuroprotective pathways, reinforced by concordant metabolomic signatures. Seahorse further confirmed that ME-ENPs trigger adaptive metabolic reprogramming, marked by a glycolytic shift and increased RGC bioenergetic output. **Conclusion** ME-ENPs outperform the crude preparation and other fractions by more effectively restoring RGC bioenergetics and metabolic resilience, providing superior neuroprotection and a promising therapeutic strategy for glaucoma.

Disclosures: S.K. Vishwakarma: None. **M. Gedda:** None. **D. Kumar:** None. **S.I. Tomarev:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

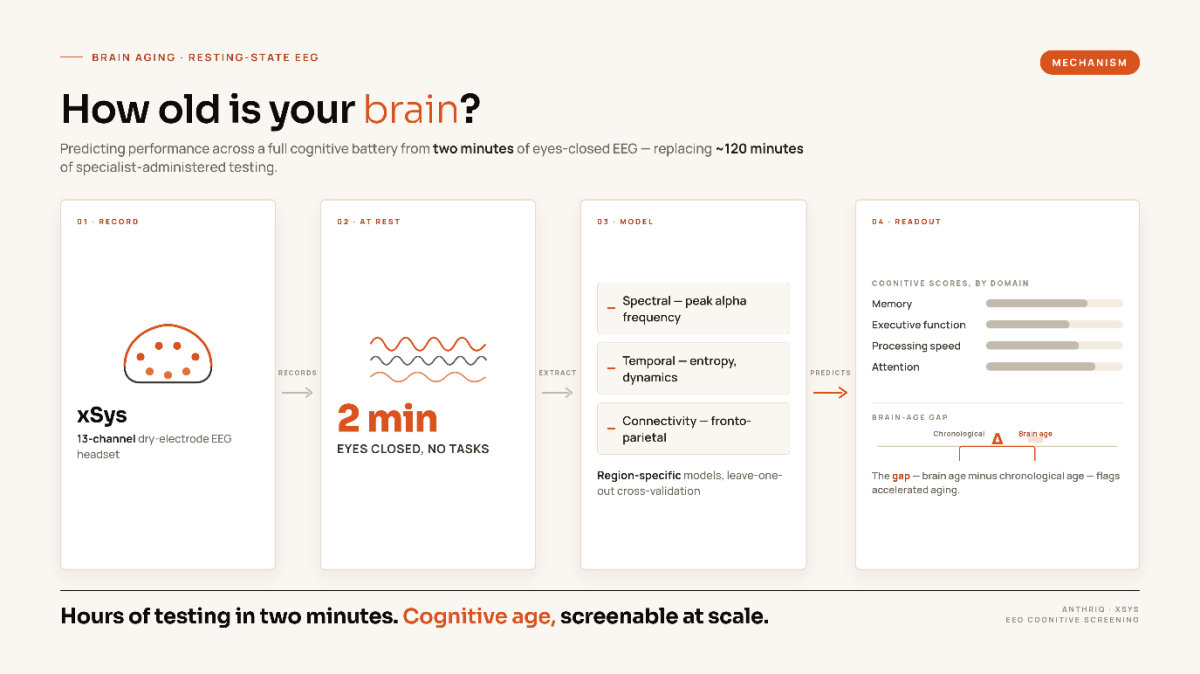
Program #/Poster #: PSTR348.13/T17

Topic: C.01. Brain Wellness and Aging

Title: How old is your brain? Predicting cognitive decline from two minutes of EEG

Authors: *S. BHATTACHARJEE;
Anthriq, Bangalore North, India

Abstract: The treatments that can slow cognitive decline — anti-amyloid drugs, brain stimulation, cognitive training — work only at its earliest stages, so detection, not therapy, is the bottleneck. Decline begins up to two decades before diagnosis, yet over 55 million people live with dementia, a figure doubling every 20 years, and only one in six ever receive an early MCI warning. Catching it early today still means a ~120-minute neuropsychological battery that requires a specialist and cannot scale to the populations that need it. At Anthriq we build research-grade EEG hardware, and we are using it to test a direct question: can two minutes of eyes-closed, task-free EEG predict performance across a full cognitive battery? This is an experiment-driven program: we acquire resting-state recordings using xSys, Anthriq's 13-channel dry EEG system, extract features (spectral, temporal, and connectivity), and train models that estimate cognitive scores and brain age, using region-specific electrodes and leave-one-out cross-validation with age as a covariate. Models trained on 126 subjects were tested on an external hospital dataset. Four findings stand out. First, Peak Alpha Frequency (C-PAF, N-PAF) stays correlated with cognition after controlling for age (NART $\rho = -0.42$, $p = 0.001$; QMCI $r = 0.31$, $p < 0.05$) — it tracks brain aging, not just time. Second, our models predict brain age to within 4.33 years (mean absolute error) on external data. Third, the theta/alpha ratio at Fz is the strongest marker of executive control. Fourth, fronto-parietal connectivity, not local power, dominates global-cognition prediction. We are now collecting data on our own EEG devices to push toward predicting the full battery from resting EEG alone, with early results approaching task-based accuracy. The end goal of this project is a device-and-algorithm system that flags early cognitive decline economically and at scale, anywhere.



Disclosures: S. Bhattacharjee: A. Employment/Salary (full or part-time):; Head of Research at Anthriq.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.14/T18

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 RF1AG081767
R01 NS122805-03

Title: The effects of sub-anesthetic ketamine on interactions between principal neurons and interneurons in the ventral posteromedial nucleus of the thalamus

Authors: *Y. M. M. SURTCHEV[1], A. WHITE[1], G. HOLGUIN[2], A. TAPIA[3], Z. HUESTIS[4], K. BOONE[3], C. A. BARNES[5], T. FALK[1], S. L. COWEN[6];
[1]Dept. of Neurosci., [2]Psychology, [4]Dept. of Biochem., [5]Evelyn F. McKnight Brain Inst., [6]Dept. of Psychology, [3]Univ. of Arizona, Tucson, AZ

Abstract: Sub-anesthetic ketamine can be an effective treatment for treatment-resistant depression and post-traumatic stress disorder. Evidence from our group also suggests ketamine reduces levodopa-induced dyskinesias associated with the treatment of Parkinson's disease. Prior analysis of motor cortex neural ensemble data suggests that ketamine reorganizes fast-timescale

(<100 ms) neuron-to-neuron interactions (Vishwanath et al. 2025), a network-level property that may contribute to ketamine's dissociative and therapeutic effects. It remains unclear whether this reorganization extends to subcortical structures or if this effect differs by neuronal subtype (e.g., principal cells vs interneurons). The ventral posteromedial nucleus (VPM) of the thalamus processes and relays trigeminothalamic somatosensory input from the head and face. Glutamatergic and GABAergic neurons in the thalamus express NMDA receptors (NMDARs), which regulate synaptic integration, plasticity, and burst firing. Ketamine may impact these properties through its function as an NMDAR antagonist and multifunctional ligand. Furthermore, ketamine's effects may be selective to parvalbumin-expressing (PV) GABAergic interneurons in the thalamus as PV neurons have a high affinity for ketamine. We hypothesized that ketamine would (1) reconfigure fast-timescale (<100 ms) neuron-to-neuron interactions in the VPM, similar to effects reported in motor cortex, and (2) reduce activity in putative PV interneurons while increasing activity in putative glutamatergic neurons via disinhibition. To investigate, we recorded neural ensemble activity from the VPM of freely behaving male and female Sprague-Dawley rats (N = 5) using Neuropixels probes (AP 3.35, ML 2.8, DV 5.25-6.5 mm) during open-field exploration. Animals received two injections of ketamine (20 mg/kg, i.p.) or saline, administered 2 hours apart. At present, 250 neurons have been analyzed and classified into putative PV neurons and principal cells based on waveform and firing characteristics. Preliminary analysis revealed that ketamine induced (1) a notable reconfiguration of sub-second interactions between neurons and, contrary to our prediction, (2) varied firing-rate response in both excitatory and inhibitory VPM neurons, with subsets of glutamatergic and GABAergic cells showing increased or decreased firing after ketamine injection. This suggests that the disinhibition hypothesis of ketamine action does not completely account for its effects on neuronal firing, and points to a more complex, network-driven reconfiguration of neuronal interactions within the VPM.

Disclosures: Y.M.M. Surtchev: None. **A. White:** None. **G. Holguin:** None. **A. Tapia:** None. **Z. Huestis:** None. **K. Boone:** None. **C.A. Barnes:** None. **T. Falk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TF has a patent for the use of ketamine as a novel treatment for levodopa-induced dyskinesia associated with Parkinson's disease, that was licensed to PharmaTher Inc. in October 2020. F. Consulting Fees (e.g., advisory boards); TF has consulted for PharmaTher Inc. and also received travel support in 2022. **S.L. Cowen:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.15/T19

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 RF1AG081767
NIH R01 NS122805

Title: Sub-anesthetic ketamine induces distinct and persistent neural ensemble states in the dorsal hippocampus

Authors: *A. WHITE[1], Y. M. SURTCHEV[1], G. HOLGUIN[2], K. JORGENSEN[3], A. TAPIA[3], Z. H. HUESTIS[3], S. H. MAREAN[3], K. BOONE[3], C. A. BARNES[4], T. FALK[5], S. L. COWEN[6]; [1]Neurosci., [2]Psychology, [4]Evelyn F. McKnight Brain Inst., [5]Dept. Of Neurol., [6]Dept. of Psychology, [3]Univ. of Arizona, Tucson, AZ

Abstract: Sub-anesthetic ketamine can be an effective treatment for treatment-resistant depression and post-traumatic stress disorder. Data from our group also shows ketamine reduces L-DOPA-induced dyskinesia due to the treatment of Parkinson's disease. Prior analysis of motor cortex neural ensembles from our group suggests that ketamine induces distinct neural states marked by a re-configuration of neuron-to-neuron interactions (Vishwanath et al. 2025). It remains unclear whether such effects extend to structures beyond motor cortex such as the hippocampus. The hippocampus is of particular interest given its involvement in memory, navigation, anxiety, and depression. The role of the hippocampus in memory and depression may be connected as depression is strongly associated with rumination: the repeated mental revisiting of negative memories. It is conceivable that ketamine disrupts such revisiting by reorganizing neuronal activity in the hippocampus. Consequently, we hypothesized that ketamine reorganizes neuron-to-neuron interactions and ensemble states in the hippocampus. We also predicted that these states will be sustained for at least 2 hours after ketamine injection (ketamine's half-life is ~1 hour in rodents).To examine these questions, we recorded neural ensemble activity from the dorsal hippocampus (CA1 and CA3) in freely behaving male/female Sprague-Dawley rats (N = 5) using Neuropixels probes (AP:3.35 ML:2.8 DV:2-3.5 mm). Animals received 2 injections of ketamine (20 mg/kg, i.p.) or saline, with each injection separated by 2 h. At present, 150 neurons have been analyzed and classified as putative interneurons or principal cells based on waveform shape and firing properties. Ensemble states were investigated at timescales ranging from 100-5000 ms where states were defined as either a population vector (vector of firing rates across neurons) or the pattern of neuron-to-neuron correlations during a given time interval. Preliminary analysis indicates that ketamine injection induced 2 distinct and persistent brain states. The first occurred 5-20 min post-injection and the second 25-80+ min post-injection. The emergence of the second state roughly corresponds to increases in blood concentration of norketamine (NK) and hydroxynorketamine (HNK), psychoactive ketamine metabolites that exhibit anti-depressive effects. Taken together, the preliminary results suggest that sub-anesthetic ketamine reorganizes ongoing hippocampal activity which could conceivably disrupt the replay of negative memories. Future studies using NK and HNK could resolve their involvement in the generation of the second state.

Disclosures: A. White: None. **Y.M. Surtchev:** None. **G. Holguin:** None. **K. Jorgensen:** None. **A. Tapia:** None. **Z.H. Huestis:** None. **S.H. Marean:** None. **K. Boone:** None. **C.A. Barnes:** None. **T. Falk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TF has a patent for the use of ketamine as a novel treatment for levodopa-induced dyskinesia associated with Parkinson's disease, that was licensed to PharmaTher Inc. in October 2020. F. Consulting Fees (e.g., advisory boards); TF has consulted for PharmaTher Inc. and also received travel support in 2022. **S.L. Cowen:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.16/T20

Topic: I.09. Spatial Navigation

Support: NSF CAREER 204770
NIH/NINDS R01NS136464

Title: Age- and sex-related changes of proteasome, ubiquitin, and Arc abundance in the hippocampus and their correlations to spatial learning

Authors: *A. A. MOMIN[1], D. YAKOUT[1], L. WANG[2], Z. D. ALLEN[1], A. M. MABB[1];
[1]Neurosci. Inst., [2]Georgia State Univ., Atlanta, GA

Abstract: The ubiquitin-proteasome system (UPS) tags and degrades unwanted proteins, with the 26S proteasome degrading ubiquitin-labeled substrates via its catalytic β-subunits that reside in the 20S core. Dysregulation of this system is linked to neurodegenerative diseases like Alzheimer's and Parkinson's, where cognitive impairment is a common phenotype. The immediate early gene Arc regulates synaptic plasticity by controlling activity-dependent AMPA receptor trafficking, an important molecular process that is critical for learning, memory, and cognitive flexibility. Our lab has previously shown that a knock-in mouse model that prevents Arc degradation (ArcKR) caused juvenile male mice (~p30) to exhibit cognitive inflexibility in the reversal phase of the Barnes Maze. Here, we examined whether this behavioral phenotype, associated with impaired Arc degradation, persists as age increases. While we observed sex-dependent differences in mice during the Barnes Maze performance, with adult and aged female mice relying more heavily on serial and random strategies than males, genotype-specific cognitive inflexibility was not observed in male aging ArcKR mice, indicating an age-specific washout effect in male mice. Given the lack of phenotype in aging ArcKR mice, we sought to correlate behavioral metrics with age- and sex-dependent molecular changes in hippocampal Arc, ubiquitin, and proteasome abundance. We found that proteasome abundance and activity decrease with increasing age (p7, p30, p180, p365) in both sexes. Age-dependent changes in Arc abundance show a large increase at p30 with a general decrease at p180 and p365. Future studies will focus on quantification of ubiquitin abundance to provide additional insight into how the UPS and age-related changes in protein turnover may affect Arc regulation and Arc turnover effects on cognitive flexibility.

Disclosures: A.A. Momin: None. **D. Yakout:** None. **L. Wang:** None. **Z.D. Allen:** None. **A.M. Mabb:** None.

Poster

PSTR348: Brain Health and Cognition: Mechanisms and Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.17/T21

Topic: I.05. Working Memory

Support: K25AG086592
5R25AG076396-03
Gator NeuroScholars Fellowship

Title: Comparing Isotropic and Anisotropic tDCS Modeling Using 11-Tissue Custom Segmentation in Older Adults

Authors: *K. LIANG[1], S. STOLTE[2], S. MILTENBERGER[3], S. DICK[4], T. BUSCH[2], A. QUEEN[2];
[1]Univ. of Florida, Tallahassee, FL; [2]Dept. of Clin. and Hlth. Psychology, [4]Psychology, [3]Univ. of Florida, Gainesville, FL

Abstract: Transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique delivering weak electrical currents to the brain, is studied as a cognitive intervention in older adults. While standard tDCS models typically assume isotropic conductivity (i.e., a single conductivity value per tissue), white matter exhibits anisotropic structure, with conductivity varying along its fiber tracts. However, accounting for anisotropy increases model complexity and computational cost. This study investigates whether utilizing white matter anisotropy produces meaningful differences in modeled electric fields relative to their isotropic counterparts. We also implemented our deep learning segmentation method to segment older adults' heads into 11 tissue classes since the amount of current that reaches the brain has been shown to depend largely on interindividual anatomy. Eleven segmentation labels were integrated with SimNIBS (ver 4.1.0; Puonti et al., 2020) default labels, adding extra tissue indices and reassigning tissue conductivities to incorporate 11 tissue types. For the anisotropic simulations, FSL was used to process diffusion weighted imaging data and generate conductivity tensors. Isotropic and anisotropic simulations were executed in SimNIBS for 9 participants from the AIM pilot study, a sham-controlled randomized within-participants trial evaluating tDCS effects in healthy older adults and individuals with mild cognitive impairment. Current density (J) maps were extracted for whole-brain and prefrontal regions of interest including the superior frontal gyrus (SFG), middle frontal gyrus (MFG), and inferior frontal gyrus (IFG), to assess statistical differences between the two approaches. Isotropic modeling produced consistently higher gray matter median J values across our regions of interest (SFG, MFG, IFG) compared to anisotropic models ($p < 0.01$, Wilcoxon $r > 0.8$). Anisotropic simulations yielded significantly higher median J values in the whole brain white matter ($p < 0.01$, $r > 0.8$). Anisotropic modeling significantly altered the current distribution, producing lower gray matter and higher white matter median J values relative to isotropic models. These findings suggest that incorporating anisotropy alongside our 11-tissue models, despite increased time and computational burden, may better represent age-related neuroanatomical variation, resulting in more anatomically informed tDCS simulations in older adults with and without mild cognitive impairment. We plan to increase the sample size prior to presentation to further validate our findings.

Disclosures: K. Liang: None. **S. Stolte:** None. **S. Miltenberger:** None. **S. Dick:** None. **T. Busch:** None. **A. Queen:** None.

Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.01/T22

Topic:

Support: NIH Grant UM1MH130981
Allen Institute

Title: Cell Type Diversity and Transcriptional Gradients Across the Human Medial Temporal Lobe

Authors: *A. D. GARCIA[1], Y. FU[1], D. YUAN[1], S. C. SEEMAN[1], J. L. CLOSE[2], M. HEWITT[1], W. HO[1], R. FERRER[1], K. J. TRAVAGLINI[3], N. JOHANSEN[7], T. CASPER[1], A. CHAKKA[1], N. DEE[1], J. GOLDY[4], D. L. JONES[1], B. P. LEVI[9], N. PENA[1], N. SHAPOVALOVA[1], A. TORKELSON[1], J. ARIZA TORRES[5], L. KRUSE[1], K. SMITH[1], C. D. KEENE[10], Z. YAO[8], H. ZENG[1], E. LEIN[3], T. BAKKEN[1], R. D. HODGE[6];
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Abstract: The medial temporal lobe (*MTL*), including the amygdala (*AMY*), hippocampal formation, and several neocortical association areas, facilitates many cognitive functions such as emotional regulation, learning, and memory. MTL structures are among the first and most critically debilitated regions impacted during the onset of diseases and injuries like Alzheimer's Disease and chronic traumatic encephalopathy. Here we present a comprehensive transcriptomic map of the human MTL, comprising single-nucleus RNA-seq profiles of 1.6 million high-quality nuclei across ten postmortem human donors spanning the full anatomical extent of MTL structures. We define transcriptomically unique excitatory cell types in the AMY, extended subiculum, and hippocampal formation. Several previously ambiguous types, initially annotated as "Intratelencephalic (*IT*) - Extratelencephalic (*ET*)," are reclassified as L6 IT neurons based on expression profile comparisons with multiple publicly available datasets. A rare and notable population of immature neurons is identified as originating from the paralaminar nucleus (*PL-IMNs*). These neurons emerge during adolescence, can remain immature for years, and strongly express doublecortin (*DCX*). We additionally characterize a distinct cell population from the uncus of the hippocampus, a primate-specific expansion of the anterior hippocampus homologous to the rodent ventral hippocampus. These uncal-enriched neurons are validated as regionally localized to the CA1-Subiculum using spatial transcriptomics in macaque, suggesting conservation of this cell population in primates. Additionally, transcriptional gradients within the

trisynaptic circuit, including rostro-caudal shifts in gene expression among dentate gyrus granule neurons, parallel observations from rodent studies. Annotation of MTL cell types is being undertaken as a community effort within the Brain Initiative Cell Atlas Network (*BICAN*) and members of the broader scientific community are invited to contribute.

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Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.02/T23

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

Support: U19AG060909

Title: Multiregional single-cell profiling reveals shared and specialized cellular vulnerability in Alzheimer's disease

Authors: *K. J. TRAVAGLINI[1], Y. DING[1], M. I. GABITTO[1], N. POSTUPNA[2], J. T. MAHONEY[1], A. AGRAWAL[1], E. S. KAPLAN[1], J. GOLDY[1], A. CHAKKA[1], M. XIAO[2], O. Z. KANA[1], B. R. LONG[1], H.-Y. LAI[1], N. DEE[1], E. J. MELIEF[2], J. ARIZA TORRES[1], N. M. GATTO[3], S. MUKHERJEE[2], P. K. CRANE[2], C. S. LATIMER[2], J. L. CLOSE[1], B. P. LEVI[1], K. A. SMITH[1], T. J. GRABOWSKI[2], E. B. LARSON[2], R. D. HODGE[1], J. A. MILLER[1], M. HAWRYLYCZ[1], C. D. KEENE[2], E. S. LEIN[1];
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Abstract: Alzheimer's disease (AD) is defined and staged by the progressive accumulation of amyloid-beta (Aβ) plaques and hyperphosphorylated tau (pTau) tangles across brain regions. These regions differ in architecture and function but share largely conserved cellular composition. Whether the cellular and molecular changes observed in AD in any one region generalize across the others has remained unclear. Here we extended the Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD) to ten neo- and allocortical regions spanning canonical AD staging, profiling ~7 million nuclei from 84 donors with single-nucleus RNA-seq, ATAC-seq, and Multiome alongside quantitative neuropathology and whole-genome sequencing. Nuclei were mapped to an expanded BRAIN Initiative taxonomy of 207 cell types, and a hierarchical pseudo-progression framework derived continuous, donor-level measures of AD burden within each region and across the brain from joint modeling of Aβ and pTau. Cellular changes were

highly selective and strikingly consistent: only ~30% of cell types shifted in abundance, but those that did changed in a coherent direction across regions. Specific subsets of inhibitory interneurons and myelinating oligodendrocytes were lost earliest in preclinical donors, alongside emergence of AD-associated microglia; loss of L2/3 and selected deep-layer excitatory types, sharper increases in AD-associated microglia, and emergence of reactive astrocytes followed in later-stage donors. Regionally specialized populations were also vulnerable, including expected allocortical types and, unexpectedly, primary visual cortex (V1C)-specialized layer 4 (L4 IT) excitatory neurons and intermixed Sst and Pvalb interneurons. Key cellular changes replicated across three independent cohorts of over 700 additional donors. To turn gene-level differences into testable mechanisms, we developed a multi-agent AI workflow that generates mechanistic hypotheses from transcriptomic data, grounded in the published literature. Applied to V1C-specialized L4 IT neurons, it nominated hyperexcitability as a possible convergent vulnerability phenotype. Asking whether the same molecular signatures held in pan-cortical Sst interneurons, the earliest-lost population, revealed that they too converged on hyperexcitability through distinct routes. Vulnerable Sst types also differed from unaffected ones in expression of genes prioritized by genetics, linking their vulnerability to the genetic architecture of AD. These data, available at SEA-AD.org, provide a multi-regional framework to explore other molecular and cellular changes in AD progression.

Disclosures: K.J. Travaglini: None. **Y. Ding:** None. **M.I. Gabitto:** None. **N. Postupna:** None. **J.T. Mahoney:** None. **A. Agrawal:** None. **E.S. Kaplan:** None. **J. Goldy:** None. **A. Chakka:** None. **M. Xiao:** None. **O.Z. Kana:** None. **B.R. Long:** None. **H. Lai:** None. **N. Dee:** None. **E.J. Melief:** None. **J. Ariza Torres:** None. **N.M. Gatto:** None. **S. Mukherjee:** None. **P.K. Crane:** None. **C.S. Latimer:** None. **J.L. Close:** None. **B.P. Levi:** None. **K.A. Smith:** None. **T.J. Grabowski:** None. **E.B. Larson:** None. **R.D. Hodge:** None. **J.A. Miller:** None. **M. Hawrylycz:** None. **C.D. Keene:** None. **E.S. Lein:** None.

Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.03/T24

Topic:

Title: Ast GRM3 Astrocytes Selectively Upregulate Synaptic Gene Programs in Association with Tau Pathology and Cognitive Decline in Alzheimer's Disease

Authors: *K. THUMAR, H. MATHYS;
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Abstract: Astrocytes are transcriptionally heterogeneous glial cells that regulate neuronal signaling and synaptic function, yet whether distinct astrocyte subtypes exhibit differential responses to Alzheimer's disease (AD) pathology remains unclear. Using single-nucleus RNA-sequencing data from the Religious Orders Study and Memory and Aging Project (ROSMAP),

we characterized three astrocyte subtypes (Ast GRM3, Ast CHI3L1, and Ast DPP10) and examined subtype-specific transcriptional responses across Braak stages. Pseudobulk differential expression analysis (muscat, edgeR) comparing high (5-6) versus low (0-2) Braak stage donors revealed divergent transcriptional programs across subtypes, with Ast GRM3 preferentially upregulating synaptic and excitability-related genes. Gene Ontology enrichment analysis of Ast GRM3 upregulated genes identified significant overrepresentation of trans-synaptic signaling, modulation of chemical synaptic transmission, membrane potential regulation, and potassium ion transport (Benjamini-Hochberg adjusted $p<0.005$). To independently quantify synaptic transcriptional activity, we computed a curated six-gene synaptic module score (GRIA1, GRIA4, GRID2, NLGN1, RIMS1, DLGAP1) and calculated per-donor median scores for donors with ≥20 cells per subtype. In Ast GRM3 (n=340 donors), synaptic scores positively correlated with Braak stage (Spearman $\rho=0.11$, $p=0.039$) and neurofibrillary tangle burden ($\rho=0.14$, $p=0.009$), and inversely correlated with global cognitive performance ($\rho=-0.17$, $p=0.002$), whereas amyloid burden was not significantly associated ($p=0.76$). Elevated synaptic scores in AD versus cognitively normal donors were observed only in Ast GRM3 (Wilcoxon $p=0.003$) and not in Ast CHI3L1 ($p=0.597$) or Ast DPP10 ($p=0.504$). Sex did not significantly interact with diagnosis in predicting synaptic scores (linear model interaction $p=0.618$; male n=165, female n=175). These findings identify Ast GRM3 as a transcriptionally distinct astrocyte subtype that selectively upregulates synaptic gene programs in association with increasing tau pathology and cognitive decline. The absence of comparable changes in Ast CHI3L1 and Ast DPP10 suggests that astrocyte contributions to AD progression are subtype-specific and may preferentially involve GRM3-expressing astrocytes during synaptic remodeling.

Disclosures: K. Thumar: None. **H. Mathys:** None.

Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.04/T25

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

Title: Astrocyte Metabolic Regulatory Programs Associated with Alzheimer's Disease Pathology and Preserved Cognitive Function in Old Age

Authors: *S. GHORBANIKALATEH, S. GHORBANIKALATEH, H. MATHYS;
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Abstract: Alzheimer’s disease (AD) is characterized by widespread transcriptional remodeling across brain cell types, yet the regulatory programs associated with preservation of cognitive function in aging and Alzheimer's disease remain incompletely understood. Using a single-nucleus transcriptomic atlas from approximately 2.3 million prefrontal cortex cells obtained from 427 ROSMAP donors spanning a broad range of AD pathology and cognitive impairment, we investigated transcription factor (TF) activity programs associated with cognition,

neuropathology, and biological pathways. Donor-level pseudobulk expression profiles were analyzed across major brain cell populations, and TF activities were inferred using DoRothEA regulons and VIPER. Given prior evidence linking astrocytes to preservation of cognitive function in aging, we focused our analyses on astrocyte regulatory programs. Higher SREBF2 activity was significantly associated with better cognition in covariate-adjusted (β=0.212, FDR=0.004) models and lower neuropathological burden across multiple AD-related measures, including amyloid burden, tangles, NFT burden, Braak stage, and global pathology. To investigate biological mechanisms underlying these associations, we quantified MSigDB Hallmark pathway activities. Fatty acid metabolism and peroxisome pathways were positively associated with cognition, whereas hypoxia, coagulation, estrogen-response, myogenesis-like, and WNT/β-catenin pathways were associated with greater neuropathological burden. SREBF2 activity was strongly associated with the Hallmark peroxisome pathway, providing potential biological context for the observed association between SREBF2 activity and better cognitive outcomes. Parallel analyses across excitatory neurons, microglia, and vascular cells identified additional pathology-associated TF programs. For example, excitatory neurons exhibited pathology-associated TF signatures involving ZFX, TP53, REST, and SMAD5, highlighting broad cell-type-specific transcriptional regulatory remodeling in AD. Together, these findings identify astrocyte metabolic regulatory networks, particularly those involving SREBF2, as potential contributors to preserved cognitive function in aging and Alzheimer's disease.

Disclosures: S. Ghorbanikalateh: None. **S. Ghorbanikalateh:** None. **H. Mathys:** None.

Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.05/T26

Topic:

Title: Oligodendrocyte transcription factor-linked pathway programs associated with Alzheimer’s disease pathology and preserved cognition

Authors: *S. GHORBANIKALATEH, S. GHORBANIKALATEH, H. MATHYS;
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Abstract: Oligodendrocyte dysfunction is increasingly implicated in Alzheimer’s disease (AD), but the transcription factor (TF)-linked pathway programs associated with neuropathology and cognition remain incompletely defined. We aimed to identify oligodendrocyte TFs associated with AD pathology and cognition and to place these TF-phenotype associations in the context of Hallmark pathway programs linked to the same outcomes. Using the ROSMAP single-nucleus RNA-seq dataset reported by Mathys et al. (Cell, 2023), we integrated donor-level oligodendrocyte TF activity, MSigDB Hallmark pathway scores, and AD pathology/cognition outcomes. Hallmark-phenotype, TF-Hallmark, and TF-phenotype associations were tested using covariate-adjusted models with global FDR < 0.05. We prioritized significant TF-phenotype

associations for which the same TF was also associated with a Hallmark pathway linked to the corresponding AD pathology or cognition outcome. This analysis highlighted two oligodendrocyte regulatory patterns. First, FOXO1 was associated with greater AD pathological burden, including higher neurofibrillary tangle burden and global AD pathology. These FOXO1-phenotype associations were accompanied by positive associations between FOXO1 and disease-linked Hallmark programs, including HALLMARK_E2F_TARGETS and HALLMARK_ANDROGEN_RESPONSE. E2F target activity was associated with higher tangle burden and poorer global cognition, whereas androgen-response activity was associated with higher global pathology, higher Braak stage, and poorer cognition. Thus, FOXO1 represented the clearest pathology-associated TF, aligning higher TF activity with Hallmark programs showing adverse AD-related associations. Second, EOMES, NFATC1, and TCF3 were associated with lower tangle burden or better cognition and showed inverse associations with E2F target activity. EOMES and POU5F1 were also associated with lower pathology or better cognitive outcomes and showed inverse associations with androgen-response activity. Therefore, TFs associated with more favorable AD-related outcomes were linked to lower activity of the same Hallmark programs associated with greater pathology or poorer cognition. Together, these findings identify E2F-associated and androgen-response oligodendrocyte programs as transcriptional states linked to AD pathology and cognition, highlighting FOXO1, EOMES, POU5F1, NFATC1, and TCF3 as candidate TF-linked markers supported by disease-associated pathway relationships.

Disclosures: S. Ghorbanikalateh: None. **S. Ghorbanikalateh:** None. **H. Mathys:** None.

Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.06/T27

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

Title: Single-Cell Transcriptomic Insights into the Cardiovascular-Stroke Interface of AD/ADRD: A Systematic Review

Authors: P.-Y. CHUANG[1], ***K. BEJARANO MENDOZA**[2], A. VILLARROEL[3];
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Abstract: BACKGROUND/INTRODUCTION: Dementia and AD/ADRD are closely linked to the brain-immune-genome (BIG) clinical profile. However, matched multi-omics and compartment-specific single-cell data from large, deeply phenotyped, and standardized cohorts remain scarce. We aim to synthesize human single-cell and multi-omics studies in dementia and AD/ADRD to identify methodological gaps and define priorities for future research. METHOD: We extracted and followed the MeSH
terms for single-cell/nucleus and cytometry in human biospecimens (2000-2026). We built a cell-type/state evidence map and summarized direction of effect (increase,decrease, or mixed/no

change in AD vs. comparators) using two-sided exact binomial tests for cell states with ≥2 directional studies, following Cochrane PRISMA andSWiM guidance. Risk of bias was assessed with the Johns Hopkins Evidence-Based Practice rating plus a single-cell-specific checklist. RESULTS: 273 primary studiesmet the inclusion criteria. Microglia were the most frequently profiled cell type (92 studies), followed by astrocytes (51), monocytes/macrophages (34), endothelial cells
(33), T cells (24), pericytes (10), B cells (8), and NK cells (8). Two phenotypes reached statistical significance in direction-of-effect analyses: expansion of disease-associated microglia (DAM) and CD8+ TEMRA effector T cells (each in six independent cohorts with 100% concordance; p=0.03). A reciprocal loss of homeostatic
P2RY12+/TMEM119+ microglia showed near-significant concordance (five cohorts; p=0.06). Several additional phenotypes—reactive astrocyte expansion, lipid-associated Mic. 12/Mic. 13/LAM microglia, angiogenic endothelial subsets, and reduced endothelial cell proportions—showed qualitatively consistent effects with
perfect concordance but remained underpowered. Most B-cell, NK-cell, and border-associated macrophage states were supported by only one or two cohorts andwere not statistically testable. CONCLUSION: Direction-of-effect synthesis with binomial inference provides a defensible quantitative summary in a setting whereconventional meta-analysis cannot be applied.Author Disclosure Information:P. Chuang: None.

Disclosures: P. Chuang: None. **K. Bejarano mendoza:** None. **A. Villarroel:** None.

Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.07/T28

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

Support: NIH Grant R21MH126494
NIH Grant R01NS128535

Title: Cell-type specific Alzheimer's Disease analysis via predicted regional brain gene-expression data

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Abstract: Studying brain gene expression in Alzheimer’s Disease (AD) remains difficult as postmortem brain is difficult to access and does not represent evolving pathology. To evaluate the potential of monitoring AD progression with peripheral data, we used transcriptome-imputation to identify brain-region-specific AD-associated gene-expression differences in cohorts with blood-based transcriptome data on a single-cell level resolution. We utilized eight AD studies (777 AD cases, 779 cognitively unimpaired controls), imputing transcriptomes in 10

brain regions via the Brain Gene Expression and Network Imputation Engine (*BrainGENIE)* and deconvoluting the bulk data to single-cell resolution. The range of imputed transcripts was from 1,928 in the substantia nigra to 8,707 in the DLPFC. Hundreds of differentially expressed genes (DEGs) associated with AD were identified in nine brain regions, with anterior cingulate cortex and amygdala showing the most differential expression with 705 DEGs (17.3% of total imputed genes in the region) and 687 DEGs (1.9% of total imputed genes in the region) respectively. Most DEGs were unique to regions, as only anterior cingulate cortex and amygdala indicated statistically significant DGE overlap. Across the imputed brain regions, we found a combined total of 546 significantly up-regulated and 327 significantly down-regulated Reactome pathways. AD-associated genes were enriched in previously reported pathways such as proteostasis, mitochondrial dysfunction, immune response, protein translation, as well as potentially novel pathways such as cell-cycle regulation, chromatin organization, extracellular-matrix remodeling, small-molecule transport, organelle maintenance and autophagy, and DNA replication and repair. We observed significant yet moderate concordance between imputed AD-associated changes and those directly measured in the DLPFC and cerebellum. Future studies including longitudinal blood gene-expression data can increase the recoverable imputation landscape and further increase our understanding of AD pathogenesis and progressions. In conclusion, we demonstrated the scope and utility of brain expression imputation from the peripheral transcriptome, laying the groundwork for biomarker discovery and prospective AD studies.

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Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

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Program #/Poster #: PSTR349.08/T29

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

Title: Molecular and spatial dissection of orexinergic neuron subpopulation vulnerability in Alzheimer's Disease

Authors: *G. CHEN[1], A. SATPATI[1], G. SON[1], F. PEREIRA[1,2], R. LEITE[3,4], C. SUEMOTO[3,5], L. GRINBERG[1,3,4];
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Abstract: Sleep-wake changes is an early and common feature of Alzheimer's Disease (AD), characterized by sleep fragmentation and excessive daytime sleepiness. The lateral hypothalamic orexinergic neurons (OrxN) play a critical role in stabilizing arousal and sleep-wake transitions. They are among the earliest neuronal populations to degenerate, and their degeneration may contribute to early sleep disturbances in AD. Our previous work showed substantial OrxN loss by Braak stage I, with approximately 40% neuronal loss early in disease and only 20% of OrxN

persisting in late-stage AD. However, it remains unclear why some OrxN are selectively vulnerable while others persist through advanced disease stages. We aim to apply Visium HD FFPE spatial transcriptomics to postmortem human hypothalamic tissue spanning Braak stages 0, I, and VI, including atypical AD cases, to profile OrxN-enriched regions in the lateral hypothalamic area. Serial sections labeled for orexin-A, CP13, and related histologic markers will be used to identify preserved orexinergic regions, estimate local tau burden, and co-register imaging features with Visium spot coordinates. Spots will be classified as OrxN-enriched, adjacent, or poor, followed by unsupervised clustering and differential gene expression analysis to identify molecular subtypes and test their associations with disease stage and tau status. Preliminary work in healthy control and AD tissue has identified differentially expressed markers among orexinergic neuron subpopulations, supporting the feasibility of detecting transcriptionally distinct OrxN states. We expect these states to differ across AD progression and to reveal molecular signatures linked to early vulnerability or late resilience, including stress-response, metabolic, proteostatic, and signaling pathways. This study will establish an initial spatial transcriptomic framework for understanding selective OrxN vulnerability in AD and will provide a foundation for future studies of how local glial and metabolic environments contribute to OrxN degeneration or survival.

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Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

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

Support: Alzheimer’s Disease Research Center Designation funded by the South Carolina Department of Health and Human Services (University of South Carolina Leaders: Drs. Bonilha and Friedman).
P20GM155896, The Center for Clinical and Translational Research at the University of South Carolina (CLINTRUSC), PI: Francis G. Spinale

Title: Spatial Transcriptomics Reveals Neurovascular and Neuronal Vulnerability to Hyperlipidemia in Brain Aging and Alzheimer's Disease

Authors: *M. SARHAN[1], X. MA[2], Y. WANG[1], Y. ZHOU[1], S. QIU[2], D. FAN[1];
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Abstract: Spatial Transcriptomics Reveals Neurovascular and Neuronal Vulnerability to Hyperlipidemia in Brain Aging and Alzheimer's Disease
Mutaz Sarhan[1], Xiaokuang Ma[2], Yuzhen Wang[1], Yongmei Zhou[1], Shenfeng Qiu[2], and Daping

Fan[1]
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Hyperlipidemia is a modifiable risk factor for Alzheimer's disease (AD), yet how chronic lipid stress interacts with aging to reshape brain cell type-specific molecular programs remains poorly understood. We used Visium HD spatial transcriptomics to profile the medial prefrontal cortex (mPFC) of female triple transgenic Alzheimer's disease (3xTg-AD) mice across three groups: Young controls (Y, 6 months), old controls (O, 10.5 months), and old hyperlipidemic mice (OH, 10.5 months). Hyperlipidemia was induced by adeno-associated virus (AAV)-introduced hepatic expression of a gain-of-function PCSK9. Space Ranger v4 segmentation yielded 56,613 spatially resolved cells across 12 sections (four sections from each group). Pseudobulk differential expression (DESeq2) and GSEA were performed across O vs Y and OH vs O comparisons. Aging produced broad but moderate pathway remodeling across neuronal and glial populations. Hyperlipidemia superimposed on aging produced a more selective injury signature, preferentially affecting vascular-associated cells, oligodendrocytes, and excitatory cortical neurons. Pathway enrichment converged across these populations on mitochondrial ATP synthesis, electron transport chain activity, oxidative stress regulation, vascular transport, BBB integrity, endothelial remodeling, and TGFβ signaling. DEG decomposition revealed that vascular-associated cells carried the highest proportion of hyperlipidemia-specific transcriptional changes (nearly 70% hyperlipidemia-added genes), identifying the neurovascular unit as a primary site of lipid stress vulnerability. These findings demonstrate that hyperlipidemia does not simply accelerate brain aging but introduces a pathway-specific injury program centered on mitochondrial bioenergetics and neurovascular dysfunction. This spatially resolved atlas identifies vascular, metabolic, and endothelial remodeling pathways as mechanistic nodes linking systemic hyperlipidemia to AD-related neurodegeneration.

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Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

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Program #/Poster #: PSTR349.10/T31

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

Support: NIH U19 AG074862

Title: Reconstructing 3D cellular architecture from registered Xenium sections in Alzheimer’s disease

Authors: *F. PARYANI[1], M. TAGA[2], H.-U. KLEIN[2], P. L. DE JAGER[3], V. MENON[4]; [1]Neurol., [2]Columbia Univ. Irving Med. Ctr., New York, NY; [3]Tri Inst. MD PhD Prog, Rockefeller Univ., New York, NY; [4]Neurol., Columbia Univ., New York, NY

Abstract: Reconstructing 3D cellular architecture from registered Xenium sections in Alzheimer's disease Fahad Paryani[1], Jordan Henry[1], Hans-Ulrich Klein PhD[1], Berke Karaahmet PhD[1], Tsering Lama[1], Mariko Taga PhD[1], Ya Zhang PhD[1], Philip L. De Jager MD, PhD[1], Vilas Menon PhD[1]1.Center for Translational & Computational Neuroimmunology, Department of Neurology, Columbia University Irving Medical Center
Alzheimer's disease (AD) is characterized not only by amyloid plaques and tau pathology, but also by local reorganization of cellular signatures in the surrounding tissuearchitecturesurrounding tissue architecture. To better resolve these spatial changes, we developed a workflow through our BRAIN CASCADE program using the Xenium platform with 480 custom genes selected from prior single-nucleus RNA-seq analysis. Our cell type analysis workflow integrates section-level preprocessing, cross-section registration, 3D reconstruction, and downstream cell type, subtype, and neighborhood analyses across serial tissue sections from 30 individuals in the ROSMAP cohort. Using this framework, we were able to recover major cell classes from the Xenium panel and extend these mappings to finer subtype-level resolution. These assignments matched known biological patterns, including restricted expression of subtype-associated markers, layer-enriched distributions across glutamatergic neuronal populations, and enrichment of CD44-positive astrocytic populations in white matter. The analysis also detected regional enrichment and depletion of key cell populations in proximity to AD pathology. This workflow enables direct testing of hypotheses that pathological inclusions are associated with local increases in specific microglial and astrocytic subtypes and with broader shifts in surrounding cellular organization. In addition, neighborhood analyses further capture how cellular context shifts around pathology rather than treating cell types in isolation. A key advantage of the approach is that registration across serial sections sharpens spatial signal in 3D and improves comparison across cases. Patterns that are subtle in individual 2D sections become more coherent after alignment, enabling clearer interpretation of pathology-associated cellular neighborhoods. Together, these results establish a practical workflow for integrated 3D Xenium analysis in AD tissue and a foundation for testing hypotheses about cell type enrichment, depletion, and local spatial organization around pathological features.

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Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

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Program #/Poster #: PSTR349.11/T32

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

Title: Spatial tranacriptomic profiling reveals cluster-specific synaptic, lysosomal, and mitochondrial dysregulation in the Tg2576 mouse model of Alzheimer's disease

Authors: L. HOOD[1], ***C. W. BIRD**[3], M. HOENERHOFF[2];
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Abstract: The APPSWE/Tg2576 transgenic mouse model of Alzheimer's disease (AD) overexpresses a mutated human version of amyloid precursor protein (APP_{695}; KM670/671NL), resulting in age-dependent amyloid pathology and cognitive dysfunction. To further understand alterations in gene expression that may underlie AD-like functional and pathological perturbations in these mice, we applied spatial transcriptomics with cluster-stratified differential expression to localize disease-associated changes from Tg2576 mice. Coronal brain sections were collected from 10-month-old wild type and Tg2576 mice (n = 1 each) at approximately bregma -2.2 mm, containing dorsal hippocampus, as well as cortical, thalamic, and hypothalamic brain regions. These brain sections were profiled on the 10X Genomics Visium VR platform with complementary Xenium in situ profiling and visualized on the Loupe Browser. Twenty transcriptional clusters were resolved across the integrated data set. Disease vs. control differential expression was computed within each cluster, and ranked gene lists were analyzed by gene set enrichment analysis. Cluster-stratified differential expression analysis identified 2,293 differentially expressed genes (DEGs) across the 20 transcriptional clusters (adjusted $p < 0.05$, $\log_2$ fold change > 0.25). Significantly upregulated genes in Tg2576 mice compared to control mice include *App* (as expected), the hypoxia associated gene *Xlr3a*, and *Pcdhb*, a β-protocadherin family member relevant to synaptic integrity and neuronal connectivity. Significantly downregulated genes include synaptic transmission associated gene *Ccdc122* and *Gm7102*, a fibronectin pathway related gene consistent with evidence that fibronectin accumulation impairs amyloid clearance. To our knowledge, there is no previous evidence that *Xlr3a*, *Ccdc122*, and *Gm7102* are dysregulated in AD, and these may be novel candidates for involvement in the etiology of AD. Gene set enrichment analysis revealed dysregulation of pathways involved in long-term potentiation, lysosomal and autophagic function, mitochondrial function, apoptosis, epigenetic chromatin regulation, primary ciliary signaling, and glutamatergic/cholinergic neurotransmitter reuptake. Together, these findings reveal spatial dysregulation of gene expression in the brains of Tg2576 mice affecting pathways implicated in the pathophysiology of AD. Novel DEGs identified in our spatial transcriptomic assessments may provide new targets with translational potential, either by serving as early disease indicators for biomarker assessment or as interventional targets for treatment modalities.

Disclosures: L. Hood: A. Employment/Salary (full or part-time):; Inotiv, Inc. **C.W. Bird:** A. Employment/Salary (full or part-time):; Inotiv, Inc. **M. Hoenerhoff:** A. Employment/Salary (full or part-time):; Inotiv, Inc..

Poster

PSTR349: Alzheimer's Disease: Spatial Transcriptomics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.12/U1

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

Title: Spatial Transcriptomic Profiling of Neuronal and Microglial Dynamis in Tau-Injected Rhesus Monkey Hippocampus

Authors: *A. S. VURAL[1], P. D. COLEMAN[3], J. H. MORRISON[4], J. KORDOWER[2]; [1]Neurodegenerative Dis. Ctr., Arizona State Univ., tempe, AZ; [2]Arizona State Univ., Gilbert, AZ; [3]ASU-Banner Neurodegenerative Res. Ctr., Tempe, AZ; [4]UC Davis, Woodland, CA

Abstract: Spatial Transcriptomic Profiling of Neuronal and Microglial Dynamis in Tau-Injected Rhesus Monkey HippocampusAustin S Vural [1,2] Paul Coleman, John H. Morrison[3] and Jeffrey H. Kordower[1,2] 1 Arizona State University-Banner Neurodegenerative Research Center at the Biodesign Institute, Arizona State University, Tempe, AZ2 School of Life Sciences, Arizona State University, Tempe AZ3 Davis Primate Center, University of California Alzheimer`s Disease is characterized by the early accumulation of tau neurofibrillary tangles in numerous brain regions including the hippocampal formation. However, how individual hippocampal subfields (HSFs), and their cell populations, respond to tau pathology remains poorly understood. This study examined the profile of HSFs and cell type specific responses to tau propagation using the GeoMx Digital Spatial Profiler. Human P301L/S320F mutant tau was overexpressed in the left entorhinal cortex (EC) using adeno-associated viral vectors, while GFP control was injected into the right EC, allowing tau pathology to spread to Rhesus monkey hippocampus (n=6; f). Hippocampal tissues were collected at 3 (n=3) and 6 (n=3) months post-injection. Sections were hybridized with whole RNA transcriptomic atlas and stained with the neuronal marker NeuN, microglial marker Iba1, and the tau marker AT8. The geometric areas in HSFs (CA1, CA3/CA4 and dentate gyrus) were profiled from tau injected and contralateral control injected hemispheres. Regions of interest were segmented into microglia-enriched and neuron-enriched compartments, and neurons were further classified as tau-positive or tau negative based of immunofluorescence labeling. Tau-treated microglia exhibited a strong and consistent transcriptional shift characterized by an upregulation of inflammatory and stress-associated genes and downregulation of homeostatic and metabolic programs, indicating adoption of a disease-associated profile. However, there were not significant changes between HSFs. Direct comparisons of tau-positive and tau-negative cells in the tau injected site displayed similar gene expression. However, tau negative cells in the control hemisphere was different than tau negative cells in the AAV-double mutant tau hemisphere. HSFs analyses demonstrated high stress and metabolic pathway activation in the CA1 and CA3/CA4 region, whereas dentate gyrus neurons showed fewer transcriptional changes, consistent with this region’s relative resistance to tau injury. These results demonstrate that tau pathology affects the hippocampal landscape in a highly structured, revealing selective vulnerability across subfield and cell types.

Disclosures: A.S. Vural: None. **P.D. Coleman:** None. **J.H. Morrison:** None. **J. Kordower:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.01/U2

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

Support: NIH grant AG085279
NIH grant U01 AG088658

Title: Pilot metabolomic profiling of Alzheimer's disease brain tissue identifies disruption of nucleotide metabolism, redox balance, and amino acid metabolism

Authors: *Y. GO;
Emory Univ., Atlanta, GA

Abstract: Pilot metabolomic profiling of Alzheimer's disease brain tissue identifies disruption of nucleotide metabolism, redox balance, and amino acid metabolism
YM Go, V. Ly, and DP Jones

AbstractAlzheimer's disease (AD) risk and biomarker trajectories are influenced by behavioral, social, and lifestyle factors; however, the environmental chemical exposures and metabolic responses that may contribute to these differences remain largely understudied. An untargeted high-resolution metabolomics approach provides broad, hypothesis-generating coverage of metabolic perturbations, enabling the identification of metabolism interactions and biochemical signatures associated with AD. Here, we used archived cerebral cortex tissues from clinically characterized AD cases (n = 10) and cognitively unimpaired controls (non-AD, n = 10) that were obtained from Emory AD Center and analyzed for a high-resolution metabolomics study (HRM). Liquid chromatography-mass spectrometry (Q Exactive HF Orbitrap) was used for HRM, within the mass-to-charge range of 85-1275 *m/z*, ensuring high-resolution detection. To maintain analytical precision, each sample was run in triplicate. Quality control pooled reference sample (QStd3) and NIST SRM1950 were included at the beginning and end of the samples for quality control. The results show that HRM detected a total of 12,141 metabolic features separated by HILIC column chromatography in positive ion electrospray mode, of which 2,385 differed between AD and non-AD groups at FDR < 0.05. Among these, 1,143 metabolic features were lower in abundance in AD than in non-AD. These metabolites were associated with alterations in purine, histidine, methionine, and cysteine metabolism, driven by reduced levels of inosine, guanosine diphosphate, guanine, glutathione, S-adenosylmethionine, and histidine. In contrast, 1,242 metabolic features were higher in abundance in AD than in non-AD and were associated with glyoxylate and dicarboxylate metabolism and glutamate metabolism, driven by increased glyceric acid, phosphoglyceric acid, glutamine, glutamylcysteine, and succinate. In summary, these results suggest that AD is associated with broad metabolic disruption, differing between AD and non-AD groups. Metabolites with lower abundance in AD suggest impaired nucleotide metabolism, antioxidant defense, methylation capacity, and amino acid metabolism in AD. Together, these findings indicate that AD is characterized by coordinated alterations in redox balance, one-carbon/sulfur amino acid metabolism, purine metabolism, and mitochondrial-associated energy pathways.

Disclosures: Y. Go: None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.02/U3

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

Support: Cure Alzheimer's Fund
Coefficient Giving

Title: Characterizing the Metabolic Effects of Dietary Fiber Types and ApoE Isoforms in Mice

Authors: *D.-O. SEO[1], J. CHENG[2], N. CARRILLO[1], M. RODRIGUEZ-ALVARADO[1], A. ALLISON[2], J. M. LONG[2], J. I. GORDON[2], D. M. HOLTZMAN[2];
[1]Med. Col. of Georgia at Augusta Univ., Augusta, GA; [2]Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: The gut microbiome plays an important role in human metabolism, nutrition, physiology, and immune function. Accumulating evidence suggests that imbalances in the normal gut microbiome are linked to Alzheimer's disease (AD) through the regulation of microbiome-associated metabolites, such as short-chain fatty acids (SCFAs). These findings suggest that reconditioning the gut microbiome may represent a novel strategy for treating the disease.Soluble dietary fiber (SDF) is a fermentable carbohydrate found in plant-based foods that cannot be digested by human enzymes in the small intestine. However, once SDF reaches the large intestine, it can be selectively metabolized by the gut microbiota. Additionally, recent studies have indicated that Apolipoprotein E genotype (APOE) genotype, the strongest common genetic risk factor for AD, influences the structure of the gut microbiome. This raises the question of whether APOE isoforms differentially influence the impact of SDF intake on metabolism, immunity, and brain function synergistically with the gut microbiota.Here, we tested whether soluble dietary fiber could modulate gut microbiome composition and associated metabolite production in an APOE genotype-dependent manner. Mice expressing human APOE3 or APOE4 were randomly assigned to two dietary groups and fed either custom SDF-free or -rich diets for 1.5 months beginning at 2 months of age. Targeted metabolomic analysis revealed that the main SCFAs—acetate, propionate, and butyrate—were significantly higher in APOE4 mice than in APOE3 mice across diet types. (*genotype effect*, $p < 0.05$). Propionate and butyrate levels were also significantly higher in mice fed the SDF-rich diet compared with those fed the SDF-free diet (*diet-type effect*, $p < 0.05$). Additionally, 16S rRNA-based microbiome analysis revealed microbial community shifts associated with both diet type and genotype. E.g., *Romboutsia ilealis* was significantly more abundant in mice fed the SDF-free diet than in those fed the SDF-rich diet, whereas *Erysipelotrichaceae Allobaculum* was significantly more abundant in mice fed the SDF-rich diet than in those fed the SDF-free diet. Both taxa were more abundant in APOE4 mice than in APOE3 mice.Currently, we are evaluating factors involved in neuroinflammation and other brain functions and attempting to integrate these findings with microbiome and metabolome data to provide a holistic understanding of these complex interactions. Finally, we will discuss the implications of these findings for AD and future directions.

Disclosures: D. Seo: None. **J. Cheng:** None. **N. Carrillo:** None. **M. Rodriguez-Alvarado:** None. **A. Allison:** None. **J.M. Long:** None. **J.I. Gordon:** None. **D.M. Holtzman:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.03/U4

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

Support: NIH Grant RF1AG081203
Cure Alzhemimer's Fund Grant
Florida Health Grant 25A15

Title: ABCA7 deficiency alters metabolites and impairs mitochondrial function in PS19 mice

Authors: *N. WANG[1], X. HAN[2], T. KANEKIYO[3];
[1]Mayo Clin., Jacksonville, FL; [2]Univ. of Texas Hlth. Sci. Ctr. At San A, San Antonio, TX;
[3]Neurosci., Mayo Clin. Jacksonville, Jacksonville, FL

Abstract: Alzheimer’s disease (AD) is the leading cause of dementia and is characterized by amyloid-β plaques and tau neurofibrillary tangles. In addition to these hallmarks, synaptic dysfunction, mitochondrial impairment, and lipid dysregulation are increasingly recognized as important contributors to AD pathogenesis. ABCA7, an ATP-binding cassette transporter involved in lipid homeostasis and mitochondrial function, has emerged as a genetic risk factor for both early- and late-onset AD. However, its role in tau-related neurodegeneration remains unclear. In this study, we examined the impact of ABCA7 deficiency in the PS19 tauopathy mouse model. We found that ABCA7 deficiency was associated with synaptic mitochondrial dysfunction and increased levels of synaptosomal pTau231, suggesting worsened tau-associated synaptic pathology. To further define the molecular consequences of ABCA7 loss, we performed integrated lipidomic and metabolomic profiling of synaptosomes from PS19; ABCA7 knockout mice. These analyses identified convergent metabolic changes linked to tau pathology, particularly in pathways involved in brain homeostasis and energy metabolism. Together, these findings provide new insight into how ABCA7 deficiency contributes to metabolic imbalance in the brain and tauopathy, and they suggest that metabolic dysfunction may be a relevant therapeutic target in Alzheimer’s disease.

Disclosures: N. Wang: None. **X. Han:** None. **T. Kanekiyo:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.04/U5

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

Support: NIH AG085279
NIH AG088658

Title: Metabolic signatures in CSF show central failure of the urea cycle in neural aging and degeneration of Alzheimer disease

Authors: *D. P. JONES[1], Y. GO[2];
[1]Med., [2]Emory Univ., Atlanta, GA

Abstract: The urea cycle is critical to maintain neural health, supporting both elimination of excess glutamate and maintenance of arginine for nitric oxide production and protection against inflammation. Alzheimer's disease (AD) shows considerable variability due to the broad range of behavioral, social, and lifestyle factors impacting disease development. Underlying pathophysiology often involves vascular dysfunction, mitochondrial decline, and inflammation, and each of these is linked to optimal functioning of the urea cycle. While proteomic biomarkers of AD in the CSF have been extensively studied, relatively less effort has been given to elucidating metabolic signatures in the CSF which can help identify new possibilities for preventive interventions. In the present study, we performed a pilot study of archival CSF samples from the Emory AD Center for AD cases (n = 10) and controls without AD (n = 10) to test for potentially targetable metabolic signatures. Samples were extracted and analyzed by high-resolution metabolomics using hydrophilic interaction liquid chromatography (HILIC) and high-resolution mass spectrometry (Q Exactive HF Orbitrap) with positive electrospray ionization. Among the 10,520 mass spectral signals detected, 477 differed ($p<0.05$) between cases and controls. Pathway enrichment analyses showed that the 241 signals that were higher in AD were associated with glutamate and inflammatory lipid pathways, while the 238 lower in AD included the arginine pathway and polyamine metabolism. Because the urea cycle supports elimination of glutamate and also maintains arginine supply and polyamine metabolism, these results suggest that the urea cycle could be a therapeutic target to improve neural health and prevent age-related degeneration. Citrulline and other metabolic precursors to support urea cycle function are available as dietary supplements but have very limited evaluation for potential efficacy to delay cognitive decline or progression of AD. Thus, larger cohort studies are needed to replicate these findings and provide a foundation for research on the utility of urea cycle interventions to protect neural health.

Disclosures: D.P. Jones: None. **Y. Go:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.05/U6

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

Title: Evaluation of proteins selected for a plasma omics biomarker for Alzheimer's disease for association with risk factors and traditional CSF biomarkers

Authors: *A. KRISHNAN[1], M. LUTZ[2], O. CHIBA-FALEK[3];
[1]Dept. of Neurosci., UNC Chapel Hill, Chapel Hill, NC; [2]Dept. of Neurol., Duke Univ., Durham, NC; [3]Dept. of Genomic and Computat. Biol., Duke Med., Durham, NC

Abstract: Introduction: Current diagnostic methods for Alzheimer's disease (AD) based on neuropathological features are not as effective at early stages disease stages, motivating investigation of biomarkers associated with biological mechanisms including neuroinflammation. A recent study described the development of a biomarker panel based on microglia single-nucleus RNA-seq data translated to blood monocyte signatures that showed accuracy to diagnose AD at both early and progressed disease-stages. In this poster, we evaluate the proteins that comprise the signature for association with AD risk factors (age, APOE genotype, sex) and traditional CSF biomarkers.
Methods: A 300 Gene Panel derived from microglial single cell biomarker study comprised the candidate protein set. The ADNI SOMASCAN 7K dataset was used for the protein intensities and all other variables. A linear effects model was used to fit the log2 protein intensity to AD risk factors (disease stage, age, sex, APOE E4 gene dose) and traditional CSF biomarkers (ABETA and PTAU). The effectiveness of the proteins in determining the transition between AD-Cognitively Normal (CN) and Late Mild Cognitive Impairment (LMCI)-Early Mild Cognitive Impairment (EMCI) and their relationship with other covariates like age, gender and disease as well as their relationship biologically were assessed.
Results: For the 300 gene panel, 94 genes were represented in the proteomics data. The strongest association between the protein intensities was with p-tau: 73 proteins were FDR significant for the p-tau association with a range from 6·10-148 to 0.05 including PPP3R1, STX7 and PTPRJ. 50/94 genes were FDR significant ($p<0.05$) for the association with Ab with a range from 2·10-22 to 0.05 including STX7, VTI1A, PTPRJ and RAB1A. 43/94 proteins were FDR significant for an association with age with a range from 8·10-12 to 0.05 including STX7, USP15 and UBE2K. A strong association was observed between PPP3R1 intensity and p-Tau (6·10-148); FDR significant associations are also observed between PPP3R1 intensity and sex ($p=2·10-5$) and APOEe4 carriage ($p=2·10-4$).
Discussion: The proteins identified for the biomarker panel based on microglia single-nucleus RNA-seq data showed strong associations, with AD risk factors including age, sex and APOE E4 gene dose. Individually, the proteins were predictive for AD diagnosis and transition between stages of MCI.

Disclosures: A. Krishnan: None. **M. Lutz:** None. **O. Chiba-Falek:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.06/U7

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

Support: NCInnovation grant Bahr-NCI-127
U.S. DEVCOM Army Research Lab grant W911NF-24-1-0201
NIH grant T34-GM149434-01A1

Title: Identifying stereoselective autophagy-lysosomal modulator compounds for enhancing the neuroprotective, Aβ42-degrading cathepsin B protease

Authors: M. C. PAIT[1], M. F. ALMEIDA[3,6], M. R. CHEBAHTAH[1], J. M. RINGEL[4], M. NEGRAO AZIN[5], J. C. SCHISLER[7,8,9], *B. A. BAHR[2];
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Abstract: Over seven million people need help with Alzheimer's disease (AD) in the U.S., over fifty million estimated with progressive dementia worldwide. Pharmacological modulation of the autophagy-lysosomal pathway (ALP) to treat AD-type multiproteinopathy is a novel therapeutic strategy, with previous studies finding correlations between enhancement of the lysosomal protease cathepsin B (CatB) and improved measures of synaptic integrity and cognitive performance in models of AD and MCI. CatB was found by multiple groups to cleave Aβ42 into less amyloidogenic peptides (Mueller-Steiner et al. 2006 *Neuron* 51:703; Butler et al. 2011 *PLoS ONE* 6:e20501; Viswanathan et al. 2012 *ACS Med Chem Lett* 3:920). Interestingly, plasma CatB levels in exercising humans and monkeys correlated with improved memory (Moon et al. 2016 *Cell Metab* 24:332). Our work with peptidyl and nonpeptidic CatB positive modulators found improved clearance of Aβ and pathogenic tau species, as well as α-synuclein in the A53T Parkinson's disease mouse model, and TDP-43 in 3xTg AD mice. Early work with the weak CatB inhibitor Z-L-phenylalanyl-L-alanyl-diazomethylketone (Z-FA-DMK) and weak CatB/calpain inhibitor 2S,3S-trans-epoxysuccinyl-L-leucylamido-3-methylbutane ethyl ester (E64d) characterized them as neuroprotective positive modulators, but at higher concentrations they caused distinct synaptic decline. Their proteomics / IPA profiles in brain explants shared a sizable list of significantly reduced GPCRs, ion channel and ion channel regulatory proteins, and neurotransmitter and adenosine receptors. In contrast, a member of a recently developed SR71 series of small molecules i) had no effect on the above list or other targets on a 44-receptor safety pharmacology panel, ii) had no effects in different Ames tests, iii) positively modulated the active form of CatB in the absence of any inhibitory activity, and iv) enhanced synaptic markers and resiliency in hippocampal slice cultures. To address whether CatB positive modulation involves stereoselective drug interaction, novel analogs were designed and synthesized in their homochiral forms. The enantiomers of two distinct molecules, SR71-N56E and -N56K, were assessed in brain explants. In each case, the R enantiomer was found to be active for enhancing CatB 2.2- to 3.6-fold (EC50s = 3 - 10 μM) while the S enantiomer produced little or no

modulatory effect on the enzyme. In a second unique series of compounds, synthesis of separate enantiomers also exclusively exhibited CatB modulation by the R enantiomer. The stereoselective enhancement of active CatB was established in rat hippocampal explants and in human neuroblastoma SH-SY5Y cells.

Disclosures: M.C. Pait: None. **M.F. Almeida:** None. **M.R. Chebahtah:** None. **J.M. Ringel:** None. **M. Negrao Azin:** None. **J.C. Schisler:** None. **B.A. Bahr:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IP rights. Other; founder of Neuralkis Therapeutics L.L.C..

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.07/U8

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

Support: NIH Grant P30AG066512
NIH Grant R01AG087280

Title: The amyloid-β interactome in Down syndrome reveals molecular networks associated with Alzheimer’s disease pathology

Authors: *M. MARTA[1], L. TANG[2], D. LEITNER[1], M. THIERRY[3], F. OU YANG[4], B. UEBERHEIDE[2], T. M. WISNIEWSKI[1];
[1]Neurol., [2]Biochem. and Mol. Pharmacol., NYU Grossman Sch. of Med., New York, NY; [3]Inst. du Cerveau (Paris Brain Institute), PARIS, France; [4]Grad. Sch. of Arts & Sci., New York Univ., New York, NY

Abstract: Down syndrome (DS), caused by trisomy 21, confers a near-universal risk of developing Alzheimer's disease (AD) and provides a genetically defined context to study disease mechanisms. Proteomic analyses of amyloid-β (Aβ) plaques have identified conserved sets of plaque-enriched Aβ-associated proteins across DS and AD subtypes, establishing a framework for studying shared amyloid pathology. Here, we extend this work by defining the Aβ interactome in DS and integrating it with previously reported plaque proteomes to distinguish proteins biochemically associated with Aβ from broader plaque-enriched molecular changes. Aβ-associated proteins were isolated by co-immunoprecipitation from frozen postmortem human frontal cortex of DS cases with AD pathology (n=8) and analyzed by LC-MS/MS. Among 2,430 identified proteins, 1,679 were enriched relative to controls (fold-change ≥1.5), including 134 probable Aβ interactors (SAINT ≥0.65). A subset of probable Aβ interactors was also detected in plaque proteomes, linking biochemically Aβ-associated proteins to established plaque-enriched components. Gene Ontology analysis showed over-representation of terms related to neuronal development, synaptic organization, RNA-associated complexes, mitochondrial metabolism, and immune responses ($p<0.001$). Protein interaction network analysis resolved these proteins into

interconnected modules, including synaptic adhesion, RNA-protein, and complement-related clusters, with follow-up studies using histochemistry and proximity ligation assays to evaluate prioritized interactors such as Midkine and GPC1. Integration with plaque datasets from DS, early-onset AD, and late-onset AD showed that the DS Aβ interactome captures conserved plaque-enriched proteins while revealing additional Aβ-centered features not resolved by plaque composition alone. Together, these findings define the Aβ interactome in DS, extend proteomic frameworks for understanding Aβ-related pathology, and identify candidate pathways relevant to biomarker and therapeutic development.

Disclosures: M. Marta: A. Employment/Salary (full or part-time):; NYU Grossman School of Medicine. **L. Tang:** A. Employment/Salary (full or part-time):; NYU Grossman School of Medicine. **D. Leitner:** A. Employment/Salary (full or part-time):; NYU Grossman School of Medicine. **M. Thierry:** A. Employment/Salary (full or part-time):; Institut du Cerveau. **F. Ou Yang:** None. **B. Ueberheide:** A. Employment/Salary (full or part-time):; NYU Grossman School of Medicine. 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.; NYU Grossman School of Medicine. **T.M. Wisniewski:** A. Employment/Salary (full or part-time):; NYU Grossman School of Medicine. 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.; NYU Grossman School of Medicine.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.08/U9

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

Support: NIH R01 CA172546
NIH U01 AG032969
NIH P01 CA186866
NIH R56 AG061869
NIH R01 AG067598
NIH R01 AG074004
NIH R01 AG072599
NIH R56 AG072599
NIH RF1 AG071805
Internal P30 CA008748
Internal SCR_027811
Internal SCR_027802
Internal SCR_027801

Title: Introducing dysfunctional Protein-Protein Interactome (dfPPI) - A platform for systems-level protein-protein interaction (PPI) network dysfunction investigation in disease

Authors: *S. CHAKRABARTY[1], S. WANG[2], T. ROYCHOWDHURY[2], A. RODINA[3], H. ERDJUMENT-BROMAGE[5], S. D. GINSBERG[6], G. CHIOSIS[4];
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Abstract: Alzheimer's disease (AD) unfolds over decades, yet the systems-level mechanisms by which molecular stress results in synaptic failure and cognitive decline remain unresolved. Most genomic, transcriptomic and abundance proteomic studies identify what molecules are present or altered in amount, but they rarely reveal where proteins are redistributed or which partners they engage in native disease tissue. This gap is critical because cellular function is executed through protein-protein interaction (PPI) networks, and chronic AD stressors can remodel these networks before large protein abundance changes are detectable. Here we present the dysfunctional Protein-Protein Interactome (dfPPI) methodology and the dfPPI Analysis Platform for PPI rewiring-focused interaction-state proteomics. dfPPI takes advantage of disease-associated changes in protein interaction states, enriches rewired protein assemblies from native tissue, uses LC-MS/MS to identify engaged proteins, and applies a validated bioinformatics pipeline to map altered connectivity, pathway modules, and functional vulnerabilities. Applying dfPPI principles to AD supports the concept that network dysfunction is not simply a late consequence of degeneration. Rather, AD-associated stress is accompanied by broad PPI rewiring that affects synaptic plasticity and other neuronal support processes, including metabolism, immune/inflammatory signaling, translation, trafficking, cell communication, and cell-cycle pathways. These interaction-state changes can emerge early, evolve across the disease continuum, and provide a connectivity-based view of vulnerability not captured by protein abundance alone. Thus, dfPPI moves AD analysis from focus on altered protein expression toward maps of disease-associated network states and functional modules. The dfPPI Analysis Platform translates this workflow into an accessible web interface with standardized preprocessing, dfPPI-specific transformation, normalization, missing-value handling, differential interaction-engagement modelling, and pathway/network interpretation using literature-validated defaults. Users receive network-centric outputs including pathway rewiring maps and interaction-state vulnerability profiles as interactive visualizations and downloadable results. Built-in example datasets and stepwise help allow immediate exploration of biology. Together, dfPPI provides an actionable framework for identifying disease-stage, pathway, and cellular vulnerabilities missed by abundance-centric omics.

Disclosures: S. Chakrabarty: None. **S. Wang:** None. **T. Roychowdhury:** None. **A. Rodina:** None. **H. Erdjument-Bromage:** None. **S.D. Ginsberg:** None. **G. Chiosis:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.09/U10

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

Support: NIA U54 AG054349
NINDS 5T32NS121727-04

Title: Proteomic and phosphoproteomic profiling reveals conserved, human-concordant Alzheimer's disease signatures in humanized MODEL-AD mice

Authors: *N. E. KWANG[1], G. R. TAKAHASHI[1], G. MILINKEVICIUTE[1], A. GOMEZ ARBOLEDAS[2], G. MACGREGOR[1], K. N. GREEN[4], V. SWARUP[3];
[2]Mol. Biol. and Biochem., [3]Neurobio. and Behavior, [1]Univ. of California, Irvine, Irvine, CA;
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Abstract: Background. Quantitative proteomics and phosphoproteomics of post-mortem human Alzheimer's disease (AD) cortex have defined robust, disease-associated protein co-expression networks and altered phosphorylation signaling that track closely with neuropathology and cognitive decline. Because proteins represent the most directly druggable layer of disease biology, establishing whether mouse models reproduce these protein-level changes is essential. Yet, cross-species concordance in AD has been assessed almost entirely at the transcriptomic level, which is often a poor predictor of protein changes. Whether humanized AD mouse models faithfully recapitulate the human AD proteome and phosphoproteome remains largely untested. Methods. We performed deep quantitative proteomic and phosphoproteomic profiling of whole cortex from next-generation humanized AD mouse models (MODEL-AD2), which carry humanized Aβ-coding sequences within the endogenous *App* locus (harboring Swedish and Iberian variants) together with humanized *MAPT* and *APOE4* alleles, across genotypes from 4 to 24 months. Using tandem mass tag labeling with phosphopeptide enrichment and mass spectrometry, we achieved proteome- and phosphoproteome-wide quantification across samples. Protein and phosphosite co-expression networks were constructed and systematically compared with human AD cortical proteomic and phosphoproteomic datasets to compare disease-associated changes. Results. We observed widespread, progressive remodeling of the cortical proteome and phosphoproteome with disease genotype and age, with coordinated changes in functional modules linked to synaptic signaling, lipid and energy metabolism, immune and complement activation, and proteostasis. Cross-species comparison revealed high correlation between mouse and human AD, with strong preservation of human disease-associated co-expression modules and consistent directionality of differentially abundant proteins and phosphosites. Phosphoproteomic analysis revealed conserved dysregulation of kinase signaling and disease-relevant phosphorylation, including tau and other AD-associated substrates. Conclusions. Whole-cortex proteomic and phosphoproteomic profiling demonstrates that MODEL-AD2 mice reproduce the human AD proteome and phosphoproteome, undergoing widespread and human-concordant protein-level remodeling. By extending cross-species validation from the transcriptome to the functional and druggable protein and signaling layers,

these data establish MODEL-AD2 mice as a validated preclinical model for mechanistic studies and therapeutic testing in AD.

Disclosures: N.E. Kwang: None. **G.R. Takahashi:** None. **G. Milinkeviciute:** None. **A. Gomez Arboledas:** None. **G. MacGregor:** None. **K.N. Green:** None. **V. Swarup:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.10/U11

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

Support: Alzheimerfonden
KID funding- Karolinska Institutet
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Demensfonden
Frimurarestiftelsen
Margaretha af Ugglas stiftelse
Petrus och Augusta Hedlunds stiftelse
Gamla Tjänarinnor
Stohnes Stiftelsen

Title: Subcellular proteome characterization of Alzheimer's disease vulnerable neurons in a mouse model of amyloid pathology

Authors: *C. TSAGKOGIANNI[1], J.-P. ROUSSARIE[2], P. RODRIGUEZ RODRIGUEZ[1]; [1]Div. of Neurogeriatrics, NVS, Karolinska Institutet, Stockholm, Sweden; [2]Anat. & Neurobio., Boston Univ. Chobanian and Avedisian Sch. of Med., Boston, MA

Abstract: Selective neuronal vulnerability is a characteristic of many neurodegenerative disorders. In Alzheimer's disease (AD), the first neurons to degenerate are neurons in the entorhinal cortex layer II (ECII). Despite their relevance in the disease's development and progression, the mechanisms that render ECII neurons selectively susceptible remain unclear. Transcriptomic studies have outlined the early molecular changes in AD, but fail to capture the subcellular processes that contribute to neurodegeneration at the protein level. To tackle this question, we developed an in vivo system for cell-type specific and spatially resolved proteomics profiling of EC neurons. Using TurboID, a bio-engineered biotin ligase, we have generated AAVs expressing TurboID fused either to a nuclear export signal or synaptophysin, to target the somatodendritical and presynaptic compartments of EC neurons respectively. The expression of these constructs is dependent on the synapsin promoter, for neuron-specific expression.Using this approach, we set out to investigate how amyloid pathology shapes the subcellular proteome of neurons in the entorhinal cortex, generating one of the first proteomics datasets of this selectively vulnerable neuron population *in vivo*. We characterised EC neurons in male APP^{NL-F}

knock-in mice, a model of amyloid pathology that expresses the amyloid precursor protein with two pathogenic mutations, at three timepoints (3, 6, and 18 months old). This approach captures proteome changes across different stages, from pre-plaque stages through established pathology and cognitive impairment. Early findings point towards compartment-specific changes, with alterations in pathways related to axonal transport and vesicle-related processes. Together, this gives a picture of how the somatodendritic and presynaptic proteomes of the neurons of the entorhinal cortex change as amyloid pathology progresses, with the aim of identifying molecular drivers of their selective vulnerability and potential therapeutic targets for AD.

Disclosures: C. Tsagkogianni: None. **J. Roussarie:** None. **P. Rodriguez Rodriguez:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.11/U12

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

Support: AMED-PRIME JP24gm6910013
AMED-MS7 JP24zf0127010

Title: Spatial Proteogenomic Analysis of Human Alzheimer’s Disease Brains

Authors: *G. OHTSUKI[1], M. HIKOSAKA[1], K. UEMURA[2], M. HOSSAIN[3], M. TAKAO[4]; [1]Kyoto Univ., Kyoto, Japan; [2]Kyoto Univ. Grad. Sch. of Med., Kyoto-shi, Kyoto, Japan; [3]Dept. of Neuroinflam. and Brain Fatigue Sci., Grad. Sch. of Med. Sciences, Kyushu Univer, Fukuoka-Shi, Japan; [4]Dept. of Lab. Med., Natl. Ctr. Hospital, Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan

Abstract: Recent single-cell transcriptomic analyses of dementia brains and translational studies using animal models have demonstrated the involvement of tau pathology, amyloid accumulation, blood-brain barrier dysfunction, and disease-associated microglia/macrophages in Alzheimer's disease. These findings suggest the therapeutic potential of targeting these pathological processes. However, comprehensive spatially integrated analyses of RNA and protein expression at single-cell resolution in the human brain remain limited. To address this gap, we generated serial tissue sections from multiple brain regions of patients with Alzheimer's disease and neurologically normal controls (n = 12 in total) and performed spatial transcriptomic, spatial proteomic, and histopathological analyses. We successfully established a multiplexed antibody imaging mass spectrometry platform capable of simultaneously detecting 39 proteins (Hyperion XTi^{TM}, Standard BioTools). Using nuclear and cell membrane markers for cellular segmentation, approximately 120,000 cells were identified (CosMx^{TM}, Bruker Spatial Biology). However, only about 10% of cells could be reliably matched as corresponding cells across adjacent serial sections. Ongoing analyses aim to identify patient-specific cellular clusters, characterize their spatial distribution, and determine their associations with APP and tau

deposition. Furthermore, we seek to elucidate the discordant dynamics between transcriptomic and proteomic expression patterns within the diseased human brain. This study was conducted with approval from the institutional ethics committee (Kyoto University Hospital, Approval No. R5105).

Disclosures: G. Ohtsuki: None. **M. Hikosaka:** None. **K. Uemura:** None. **M. Hossain:** None. **M. Takao:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.12/U13

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

Title: Longitudinal Plasma Proteomic Profiling over Decades Reveals Sequential Biological Changes Preceding Alzheimer’s Disease, and an Investigational NLRP3 Inflammasome Inhibitor Shifts The Risk Signatures Toward Protection

Authors: N. SHAH[1], L. KLARIC[1], J. RODGERS[1], *C. PATIL[1], T. BRAUN[2], K. KALLEBERG[2], A. SORAAS[2], E. ZOTCHEVA[3], G. SELBAEK[3], P. LEONG[1], E. MORGEN[1], K. FORTNEY[1];
[1]BioAge Labs, Emeryville, CA; [2]AgeLabs AS, Oslo, Norway; [3]Norwegian Natl. Ctr. for Ageing and Hlth., Tønsberg, Norway

Abstract: Alzheimer’s disease (AD) develops over decades, yet its pre-diagnostic biology is poorly characterized. Most cohorts sample each person once, conflating lifelong risk markers with disease-proximal change, and few studies capture the health-to-disease transition to link biology to a tractable drug mechanism. We addressed both gaps in two complementary cohorts. In the HUNT cohort, we profiled plasma from 6,264 individuals using the SomaScan V5 ~11,000-protein assay at three exams (mean ages ~55, 66, 74y), spanning a median of 24, 13, and 4 years before incident AD ascertained from health registries and systematic dementia assessment. Forty-five proteins were associated with future AD decades pre-diagnosis (FDR < 0.05), with distinct proteins emerging per window and effect sizes increasing closer to diagnosis. Among individuals at high risk of developing AD based on established risk factors (age, sex, APOE-ε4 status, education, obesity, smoking, alcohol use, hypertension, diabetes and kidney function), we identified proteins involved in stress-response pathways associated with AD-resilience two decades before diagnosis, alongside susceptibility proteins implicating neuroinflammatory priming such as NLRP3 pathway activation. In a Phase-1 clinical trial enrolling participants with obesity and elevated C-reactive protein, we profiled plasma before and after 14 days of an investigational oral NLRP3 inflammasome inhibitor (BGE-102, 120 mg). Using gene set enrichment analysis, we tested whether the drug’s proteomic signature overlapped with AD-risk signatures. NLRP3 inhibition shifted the AD-risk proteome toward protection: proteins it raised were enriched among AD-protective proteins and proteins it

lowered among AD-risk proteins. This pattern was consistent across future and concurrent AD, mild cognitive impairment, and cognitive-test scores (future-AD normalized enrichment score -2.33 and +1.78; p=1.0e-10 and 1.4e-3). Following individuals longitudinally over decades resolves pre-diagnostic biology that single-timepoint studies cannot, and the convergence of an NLRP3-linked susceptibility signature with a clinical-stage NLRP3 inhibitor whose proteomic signature opposes the AD-risk proteome nominates i

Disclosures: N. Shah: A. Employment/Salary (full or part-time):; BioAge Labs. **L. Klaric:** A. Employment/Salary (full or part-time):; BioAge Labs. **J. Rodgers:** A. Employment/Salary (full or part-time):; BioAge Labs. **C. Patil:** A. Employment/Salary (full or part-time):; BioAge Labs. **T. Braun:** A. Employment/Salary (full or part-time):; AgeLabs AS. **K. Kalleberg:** A. Employment/Salary (full or part-time):; Agelabs AS. **A. Soraas:** A. Employment/Salary (full or part-time):; AgeLabs AS. **E. Zotcheva:** A. Employment/Salary (full or part-time):; Norwegian National Centre for Ageing and Health. **G. Selbaek:** A. Employment/Salary (full or part-time):; Norwegian National Centre for Ageing and Health. **P. Leong:** A. Employment/Salary (full or part-time):; BioAge Labs. **E. Morgen:** A. Employment/Salary (full or part-time):; BioAge Labs. **K. Fortney:** A. Employment/Salary (full or part-time):; BioAge Labs.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.13/U14

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

Title: AI-Guided High-Plex Spatial Profiling Reveals Distinct Neuroimmune Microenvironments in Alzheimer's Disease

Authors: R. W. CHO[1], J. FISHER[1], S. STRUBLE[2], G. SPANG[1], S. SPONAUGLE[1], R. HEIL-CHAPDELAINE[2], N. FERNANDEZ DIAZ GRANADOS[2], ***A. BOSE**[2];
[1]Cell Signaling Technol., Danvers, MA; [2]Leica Microsystems, Waltham, MA

Abstract: Alzheimer's disease (AD) is characterized by progressive neurodegeneration associated with protein aggregation, neuronal injury, and chronic neuroinflammation. However, the spatial organization of immune cell phenotypes and their interactions with pathological hallmarks within the AD brain remain incompletely understood. In this study, we applied high-plex spatial immunofluorescence imaging using the Cell DIVE™ platform from Leica Microsystems together with validated antibodies from Cell Signaling Technology to characterize the cellular and molecular landscape of human AD brain tissue. Multiplexed staining enabled simultaneous visualization of pathological protein aggregates, glial populations, and immune-associated cellular markers, allowing spatially resolved profiling of neuroinflammatory states within AD tissue. Spatial analysis revealed distinct tissue organization patterns, including preferential localization of pathological protein aggregates at the tissue periphery and enrichment of astrocyte- and microglia-associated phenotypes within interior regions. Artificial intelligence

(AI)-assisted segmentation and phenotyping using Aivia identified heterogeneous glial populations exhibiting variable co-expression of antigen presentation, phagocytic, inflammatory, and immune activation markers. Furthermore, immune-associated cell populations were enriched in proximity to β-amyloid plaques, suggesting localized neuroinflammatory microenvironments surrounding pathological lesions. Distinct immune-expression patterns were also observed between plaque-associated regions and plaque-distal tissue areas, highlighting regional diversity in the neuroimmune landscape. Our findings demonstrate the utility of integrating validated multiplex immunostaining workflows, high-dimensional spatial imaging, and AI-guided image analysis to investigate the complex cellular architecture and neuroimmune interactions of AD. This approach enables identification of spatially organized cellular phenotypes, immune interactions, and disease-associated microenvironments that may contribute to neurodegeneration and serve as candidate biomarkers or therapeutic targets in AD.

Disclosures: R.W. Cho: A. Employment/Salary (full or part-time):; Cell Signaling Technology. **J. Fisher:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **S. Struble:** A. Employment/Salary (full or part-time):; Leica Microsystems. **G. Spang:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **S. Sponaugle:** A. Employment/Salary (full or part-time):; Leica Microsystems. **R. Heil-Chapdelaine:** A. Employment/Salary (full or part-time):; Leica Microsystems. **N. Fernandez Diaz Granados:** A. Employment/Salary (full or part-time):; Leica Microsystems. **A. Bose:** A. Employment/Salary (full or part-time):; Leica Microsystems.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.14/U15

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

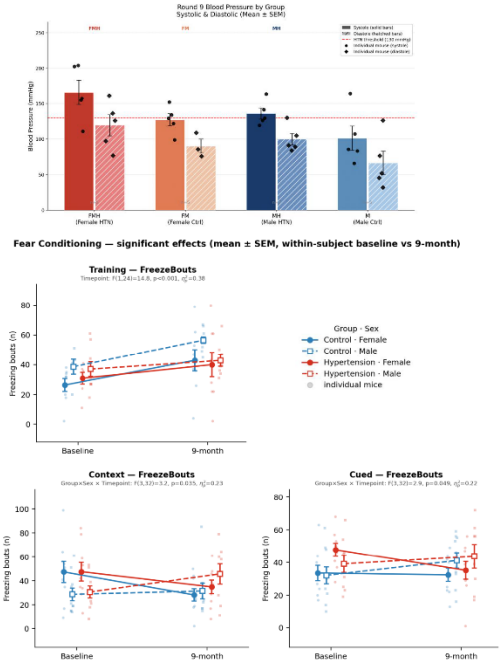
Support: UTK Graduate Student Research Awards (GSRA)
ORIED HHW grant

Title: Multimodal Evaluation of Hypertension-Induced Exacerbation of Early Alzheimer's-Related Cognitive and Neurovascular Decline

Authors: *A. JONES[1], A. CROUCH[1], J. TREMBLAY[2], E. MOODY[1], K. M. SCHULZ[3], L. RENNER[1];
[1]Univ. Of Tennessee, Knoxville, TN; [2]Psychology and Neurosci., Univ. of Tennessee Knoxville, Knoxville, TN; [3]Univ. of Tennessee, Knoxville, TN

Abstract: Alzheimer's disease (AD) is associated with vascular dysfunction, hypertension, cognitive decline, and altered brain lipid metabolism[1]. This study examines how AD, sex, and hypertension interact to shape vascular, behavioral, and lipidomic outcomes in TgSwDI mice, a transgenic model with age-related overexpression of human amyloid beta precursor protein and

vascular pathology[2]. Female and male TgSwDI mice were divided into L-NAME-treated and control groups to model chronic hypertension during disease progression. L-NAME was administered in drinking water from 3 to 6 months at 0.1 mg/g body weight with blood pressure monitored by noninvasive tail-cuff recordings. Systolic pressure in L-NAME-treated females and males exceeded the 130 mmHg threshold, while control females and males remained below it, confirming sex-differentiated hypertension induction (Fig 1). Fear conditioning at baseline and 9 months revealed intact fear acquisition across all groups using a mixed ANOVA. Significant Group×Sex×Timepoint interactions emerged in contextual and cued memory, with hypertensive females showing the greatest decline in freezing bouts while males increased across both conditions, indicating hypertension exacerbates sex-dependent memory trajectories (Fig 1)[3].Anxiety and locomotor behaviors were assessed using elevated zero and open field tests. Brains and vascular tissues were collected for mass spectrometry imaging and LC-MS lipid profiling. Lipid classes of interest include sphingomyelins, triglycerides, and lysophosphatidylcholines[4]. These findings link vascular dysfunction, lipid remodeling, and cognitive decline to define how hypertension exacerbates AD pathology in a sex-dependent manner.1 Walker "Defining the Relationship Between Hypertension Cognitive Decline and Dementia" 2 Vickle "Tg-SwDI transgenic mice exhibit novel alterations in AβPP processing Aβ degradation and resilient amyloid angiopathy" 3 Colon "Sexual differentiation of contextual fear responses" 4 Zarzar "Sex differences in the Metabolome of Alzheimer's Disease Progression"



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Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.15/U16

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

Title: Integrated Spatial Multi-Omic Profiling of Alzheimer's Disease Pathology in Human and Mouse Brain at Single-Cell Resolution

Authors: *P. CHEN[1], A. VERMA[2], Y. LYU[1], T. SHAW[3], N. PARKER[1], S. MOHAMMED GHOUSE[4], T. DEMAREST[5], S. MUKHERJEE[6], S. RAHMAN[1], L. GROOCOCK[1]; [1]Bristol Myers Squibb, Cambridge, MA; [2]Bristol Myers Squibb, Titusville, NJ; [3]Bristol Myers Squibb, Princeton, NJ; [4]Bristol Myers Squibb, Bengaluru, India; [5]Bristol Myers Squibb, Sicklerville, NJ; [6]Bristol Myers Squibb, Dundee, United Kingdom

Abstract: Alzheimer's disease (AD) is characterized by complex, spatially organized molecular alterations across diverse brain cell types that are not fully resolved by conventional bulk omics approaches. To address this, we established an integrated spatial multi-omic capability at BMS leveraging the Akoya PhenoCycler-Fusion for high-plex spatial protein profiling and 10x Genomics Visium HD for whole-transcriptome spatial mapping in FFPE human and mouse brain tissue. This approach enables simultaneous mapping of protein and gene expression at single-cell and subcellular resolution directly within preserved tissue architecture. Using this platform, we profiled control and AD human brain and mouse brain across age to define disease-associated molecular changes with spatial resolution and context not achievable using bulk methods. Spatial proteomics data confirm platform robustness and reveal cell-type-level remodeling in AD, including changes in neuronal, glial, and immune compartments. Spatially targeted niche analysis around amyloid plaques identified a distinct local molecular microenvironment, characterized by coordinated, multicellular molecular changes. Complementary spatial transcriptomics analysis identified transcriptionally distinct cell states and region-specific gene expression programs in human brain cortex. Parallel profiling in mouse brain establishes a translational framework for cross-species comparisons and studies to evaluate therapeutic interventions in preclinical models of disease. Ongoing efforts include expansion of human and mouse cohorts, integration of protein and transcriptomic data from matched tissue sections, and application of multi-omic analysis to identify spatially resolved disease signatures and novel biomarkers. Together, this integrated approach to spatial multi-omics platforms establishes a scalable foundation for AD translational research, enabling mechanistic insights, drug target validation, and biomarker discovery at single-cell resolution.

Disclosures: P. Chen: A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **A. Verma:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **Y. Lyu:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **T. Shaw:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **N. Parker:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **S. Mohammed Ghouse:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **T. Demarest:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **S. Mukherjee:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **S. Rahman:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb. **L. Groocock:** A. Employment/Salary (full or part-time):; Bristol Myers Squibb.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.16/U17

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

Title: Hyperplex Spatial Multiomics for Profiling of Neurodegenerative Landscape in an Alzheimer's Disease Mouse Model

Authors: C. SAYGILI DEMIR[1], E. BARONE[2], A. TRAMUTOLA[2], **J. KOWAL**[1], M. CASSANO[1], M. PROCOPIO[1], *S. BRAJKOVIC[1];
[1]Bio-Techne Spatial, Tolochenaz, Switzerland; [2]Sapienza Univ., Rome, Italy

Abstract: Alzheimer's disease (AD) is the most common age-associated neurodegenerative disorder, characterized by amyloid-beta (Aβ) plaque deposition, hyperphosphorylated Tau tangles, synaptic dysfunction, and metabolic impairment, ultimately leading to neuronal loss and cognitive decline (Knopman et al., 2021). While preclinical mouse models provide valuable systems to study these features, comprehensive spatial mapping of the molecular and cellular interactions underlying AD pathogenesis remains challenging. In this study, we applied a hyperplex multiomics workflow for simultaneous RNA and protein detection on the same tissue section to achieve in-depth spatial characterization of AD molecular phenotypes. Fixed frozen brain sections from triple-transgenic mice (3xTg-AD) (Pattanayak et al., 2026) and WT controls were stained and imaged on the automated COMET™ platform, integrating RNAscope™ HiPlex Pro (Wang et al., 2012) with sequential immunofluorescence (seqIF™) (Rivest et al. 2023) . Single cell quantification and spatial mapping were performed using the HORIZON™ software. The automated multiomics approach enabled simultaneous detection of over 60 markers on the same tissue section, including 12 transcripts and more than 50 protein targets, allowing the concurrent interrogation of diverse cellular populations, including neuronal subtypes, glial cells, and vascular elements, alongside markers of cellular activation, synaptic organization, and metabolic function. Complementary RNA profiling captured transcriptional programs linked to immune signaling, neuronal identity, and neuroinflammation. Tissue-wide profiling of AD brain revealed diverse molecular phenotypes, including elevated expression of astrogliosis and microgliosis markers such as GFAP, CD11c, CD45, and TSPO. Reactive microglia spatially clustered around Aβ plaques, forming localized inflammatory niches. Concomitantly, reduced mRNA expression of neurofilament genes (Nf-M and Nf-L) were detected, suggesting synaptic dysfunction. This unified RNA-protein workflow enabled comprehensive characterization of cell states and spatial organization, revealing coordinated molecular patterns across microenvironments. It captures localized shifts in immune activity, neuronal features, and vascular-metabolic signatures within a single section, providing a systems-level view of tissue organization. This automated spatial multiomics approach enables high resolution profiling of the cellular microenvironment surrounding neurodegenerative lesions, offering deeper investigation of the spatial and molecular interactions shaping AD pathology.

Disclosures: C. Saygili Demir: A. Employment/Salary (full or part-time):; Bio-Techne Spatial. **E. Barone:** A. Employment/Salary (full or part-time):; Sapienza University. Other; Did not receive any financial support, consultancy fee, honorarium, or personal compensation from Bio-Techne in relation to this work. The study was conducted as academic–industry collaboration. **A. Tramutola:** A. Employment/Salary (full or part-time):; Sapienza University. Other; Did not receive any financial support, consultancy fee, honorarium, or personal compensation from Bio-Techne in relation to this work. The study was conducted as academic–industry collaboration. **J. Kowal:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bio-Techne. **M. Cassano:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial. **M. Procopio:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial. **S. Brajkovic:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.17/U18

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

Title: From Tissue to Cell Type: Modeling the Metabolic Shifts Driven by Alzheimer's Pathology

Authors: *J. D. SEPULVEDA[1], A. V. SOLOVIEV[2], R. L. CHANG[1];
[1]Systems and Computat. Biol., [2]Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Systemic metabolic dysfunction is a defining feature of Alzheimer’s disease (AD) alongside amyloid ß (Aß) and tau protein aggregates. Systemic metabolic dysfunction remains the least understood, given the technical challenges of linking stress-associated molecular measurements, such as gene expression, to metabolic phenotypes across cell types, patients, and other clinical variables. We developed genome-scale metabolic models (GEMs) of the dorsolateral prefrontal cortex (DLPFC) of individuals with no cognitive impairment (NCI) and AD to identify changes in metabolic activity between the two conditions. GEMs are mathematical, *in silico* models of cellular metabolism and can be used to study the topology (i.e., network structure) or simulate the fluxes (i.e., activities) of all reactions in a network. DLPFC-NCI and -AD GEMs were developed by fitting a global network of human metabolism (Brunk et al., 2018) to post-mortem patient-derived transcriptomic and metabolomic data from the Religious Orders Study and Memory and Aging Project (ROSMAP) (Bennett et al., 2018) using the XomicsToModel protocol (Preciat et al., 2025). We characterized the heterogeneity of GEM network topology across all patients in both conditions using 145 NCI and 171 AD GEMs and found that network topology clearly distinguishes NCI from AD models. Differential flux analysis predicts that AD models have increased activity in amino sugar, amino acid, and sphingolipid metabolism and reduced activity in inositol phosphate metabolism, NAD metabolism, nucleotide interconversion, and pyrimidine catabolism. Finally, we delineate the

cell-type-specific metabolic response to Aß and tau aggregation using excitatory neuron (ExcN) GEMs constructed with transcriptomic data from live patient biopsies (Gazestani et al., 2023). ExcN GEMs for patients with Aβ and tau aggregates exhibit higher nucleotide interconversion and fatty acid oxidation activity, reduced peroxisomal transport, and reversed directionality of some pentose phosphate pathway reactions. Our study establishes a framework for delineating metabolic phenotypic subtypes of AD using molecular measurements across cell types, patients, and pathological events, having important implications for developing metabolic markers and further probing potentially causal metabolic shifts involved in AD development and progression.

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Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.18/U19

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

Title: Proteomic Network Analysis of Dementia Serum Identifies Key Immune and Lipid Metabolism Pathways in Egyptian Patients

Authors: *S. HEIKAL, M. M. SALAMA;
The American Univ. in Cairo, Cairo, Egypt

Abstract: Objective: Alzheimer’s disease and related dementias (ADRD) involve interacting neurobiological and systemic mechanisms, including neuroinflammation and lipid dysregulation. Proteomic data from underrepresented populations remain limited. This study characterized serum proteomic alterations and protein interaction networks in Egyptian patients with dementia to identify biologically relevant pathways associated with the disease.Methods: Serum samples from 40 participants in the Egyptian Dementia Registry (25 dementia patients, 15 cognitively unimpaired controls) were analyzed using untargeted mass spectrometry. Participants included both males and females; sex distribution was comparable across groups. Differential protein expression was assessed with multiple testing correction. A protein-protein interaction (PPI) network was constructed, followed by functional enrichment analysis. Standardized protocols were applied for sample processing and analysis, and all samples were processed under identical conditions to minimize batch effects.Results: A total of 102 differentially expressed proteins were identified and mapped into a PPI network comprising 102 nodes and 2027 edges, showing significant enrichment beyond chance (PPI enrichment < 1.0e-16) Enriched biological processes included complement activation (23/60 proteins), the acute-phase response, the humoral immune response, and the regulation of protease activity. Cellular component analysis indicated enrichment in plasma lipoprotein particles, extracellular matrix, and circulating microparticles. Pathway analysis demonstrated overrepresentation of complement and coagulation cascades, cholesterol metabolism, and platelet degranulation pathways. These findings indicate coordinated dysregulation of immune- and lipid-related pathways implicated in

neuroinflammatory and neurodegenerative processes in ADRD.Conclusions: This study provides data-driven evidence of interconnected immune and lipid metabolism alterations in dementia within an Egyptian cohort. The identified protein networks support a role for systemic inflammatory and metabolic processes in the pathophysiology of ADRD and highlight candidate biomarkers for further validation. This work represents an exploratory proteomic analysis with reproducible network-level findings in an underrepresented population.

Disclosures: S. Heikal: None. **M.M. Salama:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.19/U20

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

Support: R21AG0780705
R01AG078796
T32HL007909

Title: Impact of amyloid pathology in synaptic homeostasis across sleep-wake cycle

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Abstract: Alzheimer’s disease (AD) is a progressive brain disorder causing dementia, diagnosed post-mortem by amyloid plaques and neurofibrillary tangles. In the **early stages of AD**, amyloid-beta (Aβ) peptides are produced through the amyloidogenic processing of the amyloid precursor protein (APP) in a **synaptic activity** dependent manner. During wakefulness, learning promotes synaptic strengthening and enhances transmission, that returns to baseline levels during sleep. This **homeostatic downscaling of synapses** involves an array of cellular and molecular changes including receptor and ion channel endocytosis and the posttranslational modification of synaptic proteins. However, how amyloid pathology affects this process during sleep remain unexplored. To determine whether amyloid pathology alter synaptic proteins dynamics across the sleep-wake cycle, I harvested brains and isolated synaptosomes during the dark (active) and light (inactive) phases from WT and a knock-in mouse model of aggressive amyloid pathology $App^{NL\text{-}F;PS1/\ NL\text{-}F;PS1}$ (PS1) and performed quantitative proteomics. Our data indicates that there is robust phase-dependent remodeling of the synaptic proteome within genotypes, supporting dynamic regulation of protein abundance across the sleep-wake cycle. Comparison of protein abundance between dark and light cycles of PS1 and WT mice, showed that differentially abundant proteins differ across genotypes. This supports the notion that circadian regulation of the proteome is altered by amyloid pathology. Additionally, I hypothesize that alterations in sleep architecture are correlated with amyloid production dynamics, reflecting progressive changes as amyloid plaques

accumulate. To this end, I performed electroencephalography (EEG) recordings of WT, *App*$^{NL-F/NL-F}$(NL-F) and mice which model absent, mild, and severe amyloid pathology, respectively, to determine how increasing amyloid burden alters sleep architecture. After recovery from electrode implantation, animals underwent 48 hours of continuous recording with manual and automated scoring of wake, non-REM (NREM), and REM sleep. Across the dark phase, NL-F mice exhibited reduced percent wake accompanied by increased NREM and REM sleep relative to WT controls. NL-F animals also showed increased bout number for wake and NREM across both light and dark phases, and increased REM bout number selectively during the dark phase. Together, these findings indicate a fragmented sleep phenotype associated with amyloidogenic APP processing.

Disclosures: I. Santiago-Marrero: None. **M.H. Vitaterna:** None. **J.N. Savas:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.20/U21

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

Support: Cure Alzheimer's Fund

Title: Multi-omic analysis of APP's role in the Basal Forebrain of young and old Dp16 Down syndrome model mice

Authors: *S. SANCHEZ[1], R. L. MELTON[2], K. DANG[1], U. DAS[4], S. VOLPI[3], A. JOHNSTONE[1], Q. YANG[1], A. BECKER[1], A. WANG[1], W. C. MOBLEY[5];
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Abstract: People with Down syndrome (DS) make up the largest population genetically predisposed to developing Alzheimer's Disease (AD). Of the 6 million people living with DS, 2/3 are predicted to have dementia by the age of 65. The majority of people with DS have full trisomy 21 and thus carry an extra copy of APP, which is necessary for AD in DS. To gain unbiased insight into APP's role in AD pathogenesis in DS, we are employing a multi-omic approach in the Dp16 mouse model Basal Forebrain (BF) at young (3-5 mo.) and old (14-16 mo.) age and in euploid Dp16 mice dose-corrected for APP at the same ages. By studying both young and old mice, we are able to identify genes and pathways that are sensitive to APP dose in an age-dependent manner. We conducted paired single nuclei RNA+ATAC and single nuclei RNA-seq on 24 and 18 mice, respectively. Clustering with extensive processing and filtering of over 130,000 paired RNA+ATAC profiles and over 250,000 snRNA profiles resolved GABAergic, Glutamatergic, Cholinergic, Dopaminergic, Astrocytic, OPC, Oligodendrocytic, Microglial, and Ependymal cell types. Differential analysis of gene expression and cis-regulatory element

activity in each cell type revealed changes across genotypes and age groups in the Basal Forebrain. Within differential accessible chromatin sites, we identified TF motif binding changes for key transcription factors related to aging. At the level of RNA, we observed the expected overexpression of many trisomic genes in Dp16 mice, and a striking age-dependent bioenergetic collapse involving genes linked to mitochondrial function in GABAergic neurons, particularly at old age in Dp16 mice. In addition, normalization of APP had surprisingly far-reaching effects, normalizing the transcription of hundreds of genes. Initial investigation of mitochondrial function with Seahorse revealed that APP gene dose impacts basal respiration; deficits in oxygen consumption in Dp16 mice were corrected by APP normalization. By studying APP gene dose effects in DS, a well-defined context for AD pathogenesis, we expect to gain insights relevant to both DS-AD and AD, uncovering pathways and effectors downstream of APP that may be targeted therapeutically to prevent AD.

Disclosures: S. Sanchez: None. **R.L. Melton:** None. **K. Dang:** None. **U. Das:** None. **S. volpi:** None. **A. Johnstone:** None. **Q. Yang:** None. **A. Becker:** None. **A. Wang:** None. **W.C. Mobley:** None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.21/U22

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

Support: NIA R01AG075440 1RF1AG074256

Title: Microdose of Psilocybin in a model of Alzheimer's Disease Maintains Brain Function with Beneficial Alterations in Neuronal Transcriptome and Proteome in the Hippocampus

Authors: *S. KOTIAN;
Inst. for Regenerative Medicine, Dept. of Cell Biol. and Genetics, Texas A&M Univ., College Station, TX

Abstract: Amyloid beta plaque buildup in the early stage of Alzheimer’s disease (AD) leads to progressive increase in oxidative stress, neuroinflammation, tau phosphorylation, and neuronal dysfunction, culminating in neurodegeneration and worsened cognitive and mood function. Slowing these pathological sequelae could maintain better cognitive and mood function longer. This study demonstrated that microdoses of psilocybin (PS) could improve cognitive and mood function in 5xFAD mice by inducing beneficial transcriptomic changes in neurons, reducing neuroinflammation and adverse changes in the hippocampal proteome, and enhancing neurogenesis. Three-month-old male 5xFAD mice received monthly intraperitoneal PS (0.5 mg/kg) or vehicle for 4 months, followed by neurobehavioral testing and brain tissue analysis. PS-treated mice exhibited better object location and associative recognition memory, improved pattern separation ability, and no anhedonia. Single-nucleus RNA sequencing revealed

significant transcriptomic changes in multiple neuronal types, including glutamatergic and GABA-ergic neurons, and CA1 and CA3 pyramidal neurons. KEGG pathway analysis of differentially expressed genes (DEGs) in CA1 pyramidal neurons revealed pathways enriched for oxidative phosphorylation, AD-related, HIF-1, and apoptosis pathways, with increased expression of genes supporting better oxidative phosphorylation and reduced neuronal dysfunction and apoptosis in the PS group. In CA3 pyramidal neurons, DEGs were enriched for inositol phosphate, Ras, calcium, cAMP, and GABAergic signaling. Proteomics showed 80 proteins upregulated and 88 downregulated in the PS group compared with the vehicle-treated group. Notably, PS treatment moderated the levels of proteins involved in immune response, mTOR signaling, synapse pruning, neuron remodeling, IL-6 signaling, neuron maturation, synapse organization, and stem cell and insulin receptor signaling. Immunohistochemical and biochemical analyses showed that PS treatment reduced astrocytic hypertrophy, NLRP3 inflammasome complex in microglia, and the levels of proteins that activate the NLRP3 inflammasome and the c-GAS-STING inflammatory pathways, without impacting amyloid plaque buildup. PS also reduced mTOR activation and maintained better hippocampal neurogenesis and BDNF signaling. Thus, intermittent PS treatment induced beneficial changes in the neuronal transcriptome, proteome, BDNF signaling, and neurogenesis, and reduced activation of neuroinflammatory signaling pathways in the hippocampus, which all contribute to the overall improved cognitive and mood function in 5xFAD mouse model.

Disclosures: S. Kotian: None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.22/U23

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

Title: Convergent Cell Phenotypes and Methodological Gaps in Single-Cell Studies of Brain-Immune Network in Dementia and AD/ADRD- a Systematic Review with Direction-Of-Effect Synthesis

Authors: *P.-Y. CHUANG;
OSAH, Univ. of Maryland, Baltimore, MD

Abstract: BACKGROUND/INTRODUCTION: Dementia and AD/ADRD are closely linked to the brain-immune-genome (BIG) clinical profile. However, matched multi-omics and compartment-specific single-cell data from large, deeply phenotyped, and standardized cohorts remain scarce. We aim to synthesize human single-cell and multi-omics studies in dementia and AD/ADRD to identify methodological gaps and define priorities for future research. **METHOD:** We extracted and followed the MeSH terms for single-cell/nucleus and cytometry in human biospecimens (2000-2026). We built a cell-type/state evidence map and summarized direction of effect (increase, decrease, or mixed/no change in AD vs. comparators) using two-sided exact

binomial tests for cell states with ≥2 directional studies, following Cochrane PRISMA and SWiM guidance. Risk of bias was assessed with the Johns Hopkins Evidence-Based Practice rating plus a single-cell-specific checklist. **RESULTS:** 273 primary studies met the inclusion criteria. Microglia were the most frequently profiled cell type (92 studies), followed by astrocytes (51), monocytes/macrophages (34), endothelial cells (33), T cells (24), pericytes (10), B cells (8), and NK cells (8). Two phenotypes reached statistical significance in direction-of-effect analyses: expansion of disease-associated microglia (DAM) and $CD8^+$ TEMRA effector T cells (each in six independent cohorts with 100% concordance; p=0.03). A reciprocal loss of homeostatic $P2RY12^+$/$TMEM119^+$ microglia showed near-significant concordance (five cohorts; p=0.06). Several additional phenotypes—reactive astrocyte expansion, lipid-associated Mic. 12/Mic. 13/LAM microglia, angiogenic endothelial subsets, and reduced endothelial cell proportions—showed qualitatively consistent effects with perfect concordance but remained underpowered. Most B-cell, NK-cell, and border-associated macrophage states were supported by only one or two cohorts and were not statistically testable. **CONCLUSION:** Direction-of-effect synthesis with binomial inference provides a defensible quantitative summary in a setting where conventional meta-analysis cannot be applied.

Disclosures: P. Chuang: None.

Poster

PSTR350: Alzheimer's Disease:?Metabolomics, Proteomics, and Multi-Omics

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.23/U24

Topic: B.07. Network Interactions

Support: Cure Alzheimer's Fund
Alzheimer's Association Zeniths Fellows Award
NIH R01 AG066429
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NIH R01 AG054199
NIH R01 AG079859
NIH RF1 AG082704

Title: Discovery of neuronal extracellular vesicle-mediated interactomes in an Alzheimer's disease mouse model through TurboID-based proximity labeling

Authors: *T. IKEZU[1], B. GIBBS[2], Y. CHEN[2], M. ABDULLAH[2], B. MELVIN[2], S. IKEZU[2]; [2]Dept. of Neurosci., [1]Mayo Clin. Florida, Jacksonville, FL

Abstract: Extracellular vesicles (EVs) are critical mediators of neuronal communication and have been implicated in propagating pathological processes in neurodegenerative diseases, including Alzheimer's disease (AD). However, the molecular interactome of neuronal EVs *in*

vivo remains poorly defined. Here, we employed TurboID-CD9-based proximity biotinylation to label and capture EV-interacting proteins in the cortex of wild-type (WT) and APP^{NLGF} knock-in AD mouse models. Adeno-associated viral delivery of hSyn1 promoter-driven TurboID-CD9 enabled neuron-specific EV tagging with *in vivo* biotinylation followed by affinity purification of labeled proteins. Proteomic analysis using data independent acquisition liquid chromatography - mass spectrometry identified 5,502 proteins, with enriched pathways involving synaptic transmission and vesicle trafficking. Comparative analyses revealed robust enrichment of GABAergic signaling components, including $GABA_A$ receptor subunits (Gabrb3, Gabra1, Gabbr2), adhesion proteins (Ncam1), voltage-gated ion channels (Kcna1, Kcnc2, Kcnma1) and ion transport proteins (Slc12a5, Slc12a6), in both WT and APP^{NLGF} EV interactomes. Comparison of interactome between APP^{NLGF} and WT mice revealed enrichment of AD-associated proteins (Bin1, Scna), along with significant overrepresentation of pathways linked to action potential and membrane depolarization, including unique enrichment of Na_v channel β-subunits (Scn2b, Scn4b) and specific types of K_v channels and interacting proteins (Kcnk2, Kcnq2, Kcnip4). To understand the functional implications of these differences between our APP^{NLGF} and WT neuronal interactomes, brain derived EVs (BDEVs) were isolated from the cortex of both models through sucrose gradient ultracentrifugation and were incubated with mature human iPSC derived glutamatergic iNeurons for 24h. After incubation for 24-72 hrs, whole cell patch clamp recordings were conducted to assess the impact of BDEVs on Na_v and K_v channel activity in recipient neurons. Interestingly, cortical BDEVs isolated from the WT mice modulate the current-voltage relationship governing Na_v channel activation and inactivation compared to control groups with no EV incubation. In contrast, cortical BDEVs from APP^{NLGF} mice exhibit significantly diminished modulatory effects compared to WT BDEVs. Overall, these findings define the *in vivo* neuronal EV interactome and its remodeling in amyloid pathology, while also revealing how EVs functionally influence recipient neurons in both healthy and amyloid-burden brain microenvironments.

Disclosures: T. Ikezu: F. Consulting Fees (e.g., advisory boards); Otsuka, AAVINUE, Inc. **B. Gibbs:** None. **Y. Chen:** None. **M. Abdullah:** None. **B. Melvin:** None. **S. Ikezu:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.01/U25

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

Support: RF1NS076815

Title: ASTROCYTIC MONOACYLGLYCEROL LIPASE IS A PRECISION THERAPEUTIC TARGET FOR ALZHEIMER’S DISEASE

Authors: *M. HU;
UT Hlth. San Antonio, San Antonio, TX

Abstract: ASTROCYTIC MONOACYLGLYCEROL LIPASE IS A PRECISION THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE

Mei Hu, Li Sun, Jianlu Lyu, Dexiao Zhu, Fei Gao, Mingzhe Pan, Jian Zhang and Chu Chen

Alzheimer's disease (AD) is the leading cause of dementia worldwide. Unfortunately, effective therapies remain lacking. 2-Arachidonoylglycerol (2-AG) is an endogenous cannabinoid produced by the body that exhibits anti-inflammatory and neuroprotective properties. However, it is rapidly degraded by several enzymes, with monoacylglycerol lipase (MAGL) serving as the principal degrading enzyme in the brain. Previous studies have demonstrated that systemic inactivation of MAGL, either pharmacologically or genetically, reduces neuropathology and improves synaptic and cognitive function in AD models. However, the mechanisms by which MAGL contributes to AD pathogenesis remain unclear. Particularly, systemic inactivation of MAGL produces adverse effects in both the central nervous system and the periphery. The purpose of the present study was to determine whether 2-AG metabolism during AD development is cell type-specific. To address this question, we generated AD mouse models by crossing 5xFAD transgenic (TG) mice with global, neuron-specific, and astrocyte-specific MAGL knockout mice, generating TG-tKO, TG-aKO, and TG-nKO cohorts. We found that astrocyte-specific, but not neuron-specific, knockout of MAGL prevented learning and memory deficits, preserved synaptic structure and function, and normalized long-term potentiation. In addition, astrocyte-specific MAGL deletion markedly reduced Aβ plaque burden, attenuated neurodegeneration, and suppressed astrocytic and microglial reactivity. Transcriptomic analyses revealed that astrocytic MAGL inactivation reversed the dysregulated expression of synapse-related, immune- and inflammation-related, and AD-associated genes, restoring transcriptional profiles toward those observed in wild-type mice. Together, these findings demonstrate that 2-AG metabolism during AD development is cell type-specific and identify astrocytic MAGL as a key driver of synaptic dysfunction, neuroinflammation, and cognitive impairment in AD models. Targeting astrocytic MAGL therefore represents a promising precision therapeutic strategy to prevent or slow AD progression while avoiding the adverse effects associated with global MAGL inhibition. This work was supported by National Institutes of Health grants RF1NS076815 (to C.C.).

Disclosures: M. Hu: None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.02/U26

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

Support: Alzheimer's Association
International Society for Neurochemistry
Ciência Pioneira -IDOR
Instituto Serrapilheira
FAPERJ

Title: Deuterated polyunsaturated fatty acids blunt neuroinflammation-associated cognitive dysfunction

Authors: *B. WAGNER[1], M. CHAUVET[1], S. T. FERREIRA[2], A. R. ISAAC[3], M. V. LOURENCO[1];
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Abstract: Neuroinflammation, oxidative stress and lipid peroxidation comprise key events in neurodegenerative diseases, such as Alzheimer's disease (AD), and are associated with neuronal damage, synaptic loss and cognitive decline. Recent studies have demonstrated that bis-allylic deuteration of polyunsaturated fatty acids (D-PUFA) attenuates the chain reaction of lipid peroxidation. By strengthening the bis-allylic carbon-hydrogen bonds through the kinetic isotope effect, deuteration make PUFAs more stable and less prone to oxidation by reactive oxygen species. Therefore, D-PUFAs suppress lipid peroxidation at its earliest stages, limiting the propagation of oxidative damage and preserving membrane integrity. Moreover, D-PUFAs can favor resolvin pathways (e.g. lipoxins) in detriment of the prostaglandin synthesis, and therefore promote anti-inflammatory effects. Our group has shown that lipoxin A4 protects against cognitive decline in animal models and is reduced in the liquor of patients with dementia. Here we investigate whether a diet enriched with D-PUFAs is neuroprotective against neuroinflammation induced by LPS and transgenic AD mouse model 5xFAD.Three-month-old C57BL/6 male and female mice were fed with deuterated polyunsaturated fatty acid enriched diet (D-PUFA) or control diet (H-PUFA) for two months. Then, mice received intraperitoneal injections of LPS or vehicle. Behavior was tested by novel object recognition (NOR), displaced object recognition (DOR) and open field tasks. Five-month-old 5xFAD animals were fed with D-PUFA diet for 2 months and behavior was tested by NOR and open field tasks. All groups gained weight at the same rates during treatment and no significant difference in diet consumption was observed. Our results demonstrated that, whereas animals fed with control diet that received LPS presented deficits in NOR and DOR test, animals fed with D-PUFA diet that received LPS did not present memory impairment. 5xFAD fed with D-PUFA diet were protected from memory impairment in contrast with animals fed with control diet that presented deficit in NOR test. Our findings suggest that D-PUFA diet might be an interesting nutritional approach to mitigate neuroinflammation and cognitive decline.

Disclosures: B. Wagner: None. **M. Chauvet:** None. **S.T. Ferreira:** None. **A.R. Isaac:** None. **M.V. Lourenco:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.03/U27

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

Support: NIH R01AG069378

Title: From Gut to Brain: How Inflammation May Shape Memory

Authors: *N. KILIÇ[1], C. K. COMBS[2];
[1]Dept of Biomed. Sci., Univ. of North Dakota, Grand Forks, ND; [2]Dept of Biomed. Sci., Univ. of North Dakota Sch. of Med., Grand Forks, ND

Abstract: From Gut to Brain: How Inflammation May Shape Memory More than 3 million adults in North America live with inflammatory bowel disease (IBD), a condition marked by chronic inflammation of the gut. While IBD primarily affects the digestive system, long-term inflammation throughout the body may also impact brain health and processes linked to Alzheimer's disease (AD). In this study, we investigated how chronic intestinal inflammation affects behavior, cognition, and AD-related pathology in the *App*$^{NL-G-F}$ mouse amyloidosis model of AD and C57BL/6 wild type littermate controls. Dextran sodium sulfate (DSS)-induced colitis was used to mimic sustained inflammatory exposure in 6 month old male and female mice, and animals underwent behavioral testing to assess working and long-term memory and mobility. Overall activity and movement were preserved in DSS-treated animals, indicating that chronic inflammation did not impair motor function. Similarly, short-term working memory was unaffected by genotype or DSS treatment. However, untreated male, but not female, *App*$^{NL-G-F}$ mice exhibited reduced long-term memory performance compared to their untreated wild-type controls. Moreover, although DSS-induced colitis did not further reduce long-term memory in male *App*$^{NL-G-F}$ mice, it significantly impaired it in male WT mice compared to their untreated controls. To determine whether chronic gut inflammation also influenced AD-related neuropathology, we quantified amyloid-β (Aβ) plaque burden in the hippocampus. Chronic DSS-induced intestinal inflammation exerted sex-specific effects on amyloid pathology in *App*$^{NL-G-F}$ mice. Female mice exposed to DSS displayed increased hippocampal Aβ plaque burden relative to vehicle-treated controls, whereas males exhibited no significant increase in plaque deposition, suggesting a greater susceptibility of females to inflammation-driven amyloid accumulation. These findings suggest that chronic gut inflammation influences both cognitive function and amyloid accumulation in a sex-dependent manner. The divergent responses observed between males and females may reflect sex-specific differences in immune signaling, neuroinflammatory responses, or amyloid clearance pathways that alter communication along the gut-brain axis. Our findings provide insight into how peripheral inflammation may influence AD progression and highlight the importance of considering biological sex when investigating gut-brain interactions and neurodegenerative disease mechanisms.

Disclosures: N. Kiliç: None. **C.K. Combs:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.04/U28

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

Support: NIH Grant R21AG068532
NIH Grant T32NS115667
Pennsylvania Department of Health, TSF41000095613

Title: Elucidating the Relationship between Regional Neuroinflammation & Functional Connectivity over Alzheimer's Disease Progression

Authors: D. CHAN[1,2,4,5], ***C. KIM**[3,1,2,4], S. R. CRAMER[5], J. KANG[1,2,4], T. NEUBERGER[6], N. ZHANG[5,6], E. A. PROCTOR[1,2,4,5,6];
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Abstract: Alzheimer’s disease is a neurodegenerative disorder characterized by progressive amyloid plaque accumulation, tau tangle formation, neuroimmune dysregulation, synapse and neuron loss, and changes in neural circuit activation that lead to cognitive decline and dementia. Early molecular and cellular disease-instigating events occur 20 or more years prior to presentation of symptoms, making them difficult to study. For many years, amyloid-β, the aggregating peptide seeding amyloid plaques, was thought to be the toxic factor responsible for cognitive deficit. However, strategies targeting amyloid-β aggregation and deposition have largely failed to produce safe and effective therapies, and amyloid plaque levels poorly correlate with cognitive outcomes. However, an individual’s immune response to early, soluble forms of amyloid-β aggregates and the downstream consequences of this immune response may drive aberrant cellular behaviors and the creation of a detrimental tissue environment that harms neuron health and causes changes in activation of the neural circuits underlying cognitive processes impacted by Alzheimer’s disease. Here, we perform functional magnetic resonance imaging in an awake, unanesthetized Alzheimer’s disease mouse model to map changes in brain functional connectivity over the course of disease progression, in comparison to wild-type littermates. In these same individual animals, we spatiotemporally profile the immune milieu by measuring cytokines, chemokines, and growth factors across various brain regions and over the course of disease progression from pre-pathology through established cognitive deficit. We identify specific signatures of immune activation predicting hyperactivity followed by suppression of intra- and then inter-regional functional connectivity in multiple disease-relevant brain regions, following the pattern of spread of amyloid-β pathology.

Disclosures: D. Chan: None. **C. Kim:** None. **S.R. Cramer:** None. **J. Kang:** None. **T. Neuberger:** None. **N. Zhang:** None. **E.A. Proctor:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.05/U29

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

Support: NIH R01 AG069228
NIH RF1 AG069228
NIH R01 AG070257
CIHR CAPMC MFE-194064

Title: Dietary taurine supplementation attenuates Alzheimer's disease pathology and cognitive decline in 5xFAD mice

Authors: *C. M. TOGNONI[1,3], Z. SUAR[4,5], R. GHOSH BISWAS[4,5], I. CARRERAS[1,3,2], A. DEDEOGLU[1,3,5], B. G. JENKINS[4,5];
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Abstract: As Alzheimer’s disease (AD) continues to rise amongst the aging population, preventative measures such as dietary or lifestyle changes represent an attractive option to mitigate disease burden. Taurine, known for its antioxidant and anti-inflammatory properties, may also play a neuroprotective role. We first investigated the effects of taurine supplementation in the 5xFAD mouse model of AD administered through drinking water at doses of 0, 500, 1000, 2000, and 4000 mg/kg/day from 1-5 months of age. Postmortem markers of neuroinflammation using cytokine profiling demonstrated that 2000 mg/kg/day elicited the most favorable protective response against early AD pathology. We then evaluated treatment with 2000 mg/kg/day from 9-10 months of age, when pathology is at an advanced stage. High-resolution magic angle spinning magnetic resonance spectroscopy (HRMAS-MRS) was used to analyze and differentiate the molecular profile of three key AD-affected regions: the frontal cortex and the ventral and dorsal hippocampus. Compared to wildtype mice, 5xFAD mice exhibited significant alterations in five metabolites (GABA, glutamate, NAA, aspartate and scyllo-inositol). Taurine supplementation at 2000 mg/kg/day partially normalized levels of several metabolites, including NAA and glutamate, toward those observed in wildtype mice, suggesting neuroprotection of these neurochemicals. Cognitive behavior was evaluated using the Morris water maze (MWM). As expected, 10-month-old 5xFAD mice were significantly impaired during MWM acquisition and memory probe trials compared to wildtype mice. Taurine treatment partially rescued memory performance on multiple measures (%time in target quadrant and mean distance to target location on the 1h probe trial; pass-throughs of target location on the 24h probe trial), resulting in values that were no longer significantly different from wildtype mice. Overall, these findings

suggest that taurine supplementation may provide neuroprotective benefits across multiple stages of AD progression.

Disclosures: C.M. Tognoni: None. **Z. Suar:** None. **R. Ghosh Biswas:** None. **I. Carreras:** None. **A. Dedeoglu:** None. **B.G. Jenkins:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.06/U30

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

Support: CIHR Grant Appl. 452424
CIHR Grant Appl. 476949
NERC CREATE 546573776

Title: Humanized MAPT modulates early amyloid pathology and glial responses in App^{NL-G-F}knock-in mice

Authors: *V. LAPOINTE[1], B. B. MCALLISTER[2], A. BURGAR[1], L. FERRARI DO AMARAL[1], G. BENOIT[1], M. H. MOHAJERANI[3], V. RATHOD[4], R. J. SUTHERLAND[1]; [1]Neurosci., Canadian Ctr. for Behavioural Neuroscience, Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Psychology, Fac. of Vet. Medicine, Hotchkiss Brain Institute, Univ. of Calgary, Calgary, AB, Canada; [3]Psychiatry, Douglas Hosp. Res. Centre, McGill Univ., Montréal, QC, Canada; [4]Chem. & Biochem., Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: Alzheimer’s disease (AD), the leading cause of dementia, is characterized by progressive deterioration of memory and other cognitive abilities, adversely affecting daily life. AD is defined by amyloid-β (Aβ) deposition, tau pathology, and neurodegeneration. Neuroinflammation, involving microglia and astrocytes, is increasingly recognized as a key contributor to disease progression. Although amyloid accumulation is thought to initiate disease progression, interactions between Aβ, tau, and glial responses remain incompletely understood. *App*$^{NL-G-F}$ and h*MAPT* knock-in mouse models, which express humanized Aβ and MAPT at physiologically relevant levels and avoid artifacts associated with transgene overexpression, were used to examine whether human MAPT modifies Aβ deposition and glial responses in an age-dependent and region-specific manner. Male and female A*pp*$^{NL-G-F}$ × *hMAPT*, *App*$^{NL-G-F}$, *hMAPT*, and C57BL/6 controls mice were compared at 8, 12, and 16 months of age (n=4 per strain, age, and sex group). Aβ deposition and glial activation were assessed by immunofluorescence using 4G8 (Aβ), GFAP (astrocytes), Iba1 (microglia), and CD68 (activated microglia) in the frontal cortex, corpus callosum, and dorsal hippocampus. Across regions, Aβ pathology was restricted to mice carrying the mutant, humanized *App* allele, with the highest plaque burden observed at 8 months in *App*$^{NL-G-F}$ × h*MAPT* mice. Compared with *App*$^{NL-G-F}$

mice, *App*$^{NL-G-F}$ × h*MAPT* animals exhibited greater plaque burden and more pronounced plaque features, with some sex-dependent modulation, particularly in plaque characteristics. Astrocyte reactivity was increased in *App*$^{NL-G-F}$-containing strains, most prominently in the frontal cortex and corpus callosum at 8 months. These effects were strongest in *App*$^{NL-G-F}$ × h*MAPT* mice, while h*MAPT* mice showed minimal changes. Microglial responses were more modest but included increased cell size and CD68 expression in *App*$^{NL-G-F}$-containing strains, with effects most evident in females. Overall, Aβ deposition and glial activation were spatially convergent across cortical, white matter, and hippocampal regions, with combined *App*$^{NL-G-F}$ and h*MAPT* expression associated with greater pathological burden than *App*$^{NL-G-F}$ alone. These effects were most pronounced at 8 months and were modulated by sex and age, particularly evident in plaque characteristics and region-specific glial responses. Together, these findings suggest that human MAPT expression influences early Aβ-associated pathology and that the *App*$^{NL-G-F}$ × h*MAPT* double knock-in model captures early-stage interactions relevant to AD.

Disclosures: V. Lapointe: None. **B.B. McAllister:** None. **A. Burgar:** None. **L. Ferrari do Amaral:** None. **G. Benoit:** None. **M.H. Mohajerani:** None. **V. Rathod:** None. **R.J. Sutherland:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.07/U31

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

Support: AG069447
AG064811
AG062179

Title: Clec7a regulates sex-dependent TLR7/type I interferon signaling in Alzheimer’s disease

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Abstract: Genetic studies of late-onset Alzheimer’s disease (AD) have identified numerous risk variants that are highly expressed in microglia and enriched in innate immune pathways, highlighting a central role of immune responses in AD pathogenesis. Clec7a, a core signature gene of disease-associated microglia, is dramatically increased in the AD brain while being rarely expressed in the healthy brain. It has been shown that microglial Clec7a KO in 5xFAD mice increases amyloid beta (Aβ) plaques, suggesting the role of Clec7a in β-amyloidosis. However, the role of Clec7a in AD progression remains unclear. In this study by crossing Clec7a$^{-/-}$ mice with TgAPP/PS1 mice, we generated four experimental groups: Clec7a$^{-/-}$

TgAPP/PS1 (n=9 **F**emale & 10 **M**ale), Clec7a$^{+/+}$ TgAPP/PS1 (n=12 F &11 M), Clec7a$^{-/-}$ non-Tg (n=10 F & 11 M), and Clec7a$^{+/+}$ non-Tg (n=11 F & 10 M). Mice were euthanized at 11-12 months of age. Amyloid plaques were visualized by thioflavin S staining, and plaque burden was quantified by morphometric analysis. Soluble and insoluble Aβ were measured by ELISA. Bulk RNA-seq analysis was performed on hippocampal tissues. In addition, male Clec7a$^{-/-}$ and Clec7a$^{+/+}$ TgAPP/PS1 mice were intraperitoneally injected with TLR7 agonist, gardiquimod (GDQ, 1.5 mg/Kg bodyweight) or PBS (control) for 7 days and subjected to hippocampal bulk RNA-seq analysis. We found that Clec7a deficiency increased Aβ burden in the brains of both male and female TgAPP/PS1 mice, compared to the Clec7a wild-type (WT) cohort. TLR7 mRNA expression was elevated in both male and female Clec7a KO TgAPP/PS1 and female Clec7a WT TgAPP/PS1 mice, whereas no such increase was observed in male Clec7a WT TgAPP/PS1 mice. Furthermore, stimulation with GDQ induced a stronger type I interferon response in male Clec7a KO mice and female Clec7a WT mice, compared with male Clec7a WT mice. Consistently, GDQ further increased Aβ accumulation in male Clec7a KO mice but not in male Clec7a WT mice. Overall, these findings suggest that Clec7a plays a protective role in limiting TLR7-type I interferon signaling and its downstream pathological consequences in TgAPP/PS1 mice. In the absence of Clec7a, heightened TLR7 expression and an exaggerated interferon response, particularly in males upon GDQ stimulation, are associated with increased Aβ. These results support a model in which Clec7a restrains TLR7-driven type I interferon responses, thereby limiting Aβ accumulation in TgAPP/PS1 mice, particularly in males upon TLR7 activation.

Disclosures: J. Yang: None. **K. Fukuchi:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.08/U32

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

Title: Human APOE Isoforms Differentially Modulate Amyloid and Vascular Pathology in the Arte10 (APP:PS1) Alzheimer's Disease Mouse Model

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Abstract: Preclinical mouse models remain important tools for Alzheimer's disease (AD) drug discovery, providing insight into disease mechanisms and therapeutic responses despite limitations in translational predictability. The APOE4 allele, carried by approximately 25% of the population, is the strongest genetic risk factor for late-onset AD, increasing disease risk up to 15-fold relative to APOE3. Although many transgenic AD models express human amyloid-β,

most retain murine apolipoprotein E, which differs from human APOE in its interaction with amyloid-β. The emergence of anti-amyloid monoclonal antibody therapies has further highlighted the need for improved models, as Amyloid-Related Imaging Abnormalities (ARIA) occur more frequently in APOE4 carriers. To address this gap, we developed and characterized transgenic AD mouse models expressing human APOE3, APOE4, or murine ApoE. Arte10 mice [APPswe and PSEN1] C57BL/6NTac.CBA-Tg(Thy1-PSEN1*M146V,-APP*Swe)10Arte] were mated with human APOE4 (B6.129P2-*Apoe*$^{tm3(APOE*4)Mae}$ N8) and human APOE3 (B6.129P2-*Apoe*$^{tm2(APOE*3)Mae}$ N8) to produce HOM:HOM (APOE:Arte10) and WT:HOM animals. Animals were euthanized at 43 weeks of birth, perfused and brain collected for immunofluorescence staining. Sections were stained for amyloid-β, Iba-1, GFAP, and laminin. Using Biospective's PERMITS™ process, advanced multiplex IF staining and whole-slide images were analyzed to quantify Aβ plaque features, vascular amyloid deposition, and spatially resolved glial microenvironment responses, including microglial and astrocytic phenotypes and plaque-associated neuroinflammation. Arte10 × APOE3 and APOE4 mice showed distinct sex- and isoform-dependent patterns of amyloid pathology and associated neuroinflammation. Females exhibited greater amyloid and inflammatory burden than males across genotypes. APOE3 expression was associated with reduced amyloid-β plaque burden and a more diffuse plaque distribution, whereas APOE4 mice showed plaque counts comparable to WT Arte10 controls, along with increased vascular amyloid pathology. These findings support the translational relevance of Arte10 × human APOE models for capturing APOE-dependent features of AD pathology with direct implications for therapeutic development. By recapitulating isoform-specific differences in plaque morphology, vascular amyloid involvement, and glial microenvironment responses, these models provide a biologically relevant platform to investigate mechanisms underlying APOE-modulated disease pathology, ARIA susceptibility, and therapeutic response to anti-amyloid interventions.

Disclosures: J.R. Richardson: A. Employment/Salary (full or part-time):; Taconic Biosciences. **S.R. Sterlace:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **A. Noel:** A. Employment/Salary (full or part-time):; Biospective Inc. **M. Jacobson:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **B.J. Bedell:** A. Employment/Salary (full or part-time):; Biospective.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.09/V1

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

Support: NIA Grant R01 AG072513-01A1

Title: APOE4 drives immunometabolic exhaustion and blunts neuroprotective repair following ethanol stress

Authors: *J. KANG[1,2,3,4], C. KIM[1,3,4,2], G. BURGESS[5,2], N. A. CROWLEY[5,2], E. A. PROCTOR[1,3,4,2];
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Abstract: The ε4 variant of apolipoprotein E gene (*APOE4*) is the strongest and most common genetic risk factor for late-onset Alzheimer's disease (AD), but its specific contribution to disease onset and progression is not fully understood. Here, we examine molecular and cellular mechanisms driving the established increased risk of neurodegeneration in APOE4 carriers with alcohol use when compared to APOE3 carriers. We applied the "drinking in the dark" binge drinking paradigm in middle-aged APOE3 and APOE4 knock-in mice (12 months of age, approximately equivalent to human 42.5 years of age) to examine changes affecting brain resilience. We performed a high-throughput multiplexed immunoassay in the hippocampus from these animals and found no significant differences in neuroimmune profiles of APOE4 and APOE3 mice drinking water only. However, while mice of both genotypes experienced an increase in cytokine expression in both the hippocampus and the frontal cortex following ethanol consumption, the neuroimmune response mounted by APOE4 mice was profoundly muted following ethanol consumption in comparison to APOE3 mice, with the specific signature indicating a failure in initial damage sensing (suppressed IL-1α, IL-1β, TNF{inferred}, IL-6) and loss of trophic support (suppressed IL-2, IL-5, IL-9, IL-13, and G-CSF). This decrease in brain resilience to an acute toxin in a middle-aged brain is highly pathological. To test whether deficits in cellular metabolism may be resulting in suppressed immune function, we derived primary astrocyte cultures from neonatal (P0) APOE3 and APOE4 knock-in mouse pups and treated them with either binge-equivalent concentrations of ethanol or equivalent volume of saline. We performed extracellular flux assays and found mitochondrial oxygen consumption to be significantly and highly increased in APOE4 astrocytes as compared to APOE3 astrocytes, especially at maximal respiration, indicating high levels of oxidative stress. We performed live-cell imaging to quantify reactive oxygen species generation and found that increased mitochondrial oxidative stress was unique to APOE4 cells exposed to ethanol. Our findings suggest that the APOE4 brain experiences mitochondrial strain, and in the presence of an additional stressor like ethanol, cells expend metabolic reserves managing oxidative stress, leaving them in a state of immunometabolic exhaustion and unable to initiate cellular repair and clearance of ethanol's toxic metabolites. This decrease in brain immunometabolic resilience to alcohol use in the context of APOE4 genotype may be a strong contributor to increased risk for Alzheimer's disease in APOE4 carriers.

Disclosures: J. Kang: None. **C. Kim:** None. **G. Burgess:** None. **N.A. Crowley:** None. **E.A. Proctor:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.10/V2

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

Support: R01 AG072513-01A1

Title: APOE4 Drives a Diurnal Phase-Mismatch in Hippocampal Metabolic and Immune Kinetics

Authors: J. KANG[1,2,4,5], ***D. CHAN**[3,2,4,5,1], C. KIM[1,2,4,5], E. A. PROCTOR[1,2,4,5];
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Abstract: The ε4 variant of apolipoprotein E (APOE4) is the strongest and most common genetic risk factor for Alzheimer's disease, but its specific contribution to disease onset and progression is not fully understood in the context of daily homeostatic maintenance and biobehavioral factors. The brain relies on cyclical transitions between wake-phase activity and sleep-phase rest to manage metabolic clearance and resolve neuroinflammatory stress. Here, we investigated how APOE4 genotype influences the diurnal kinetics of the hippocampal microenvironment, and evaluated the modulatory capacity of voluntary physical activity across different stages of life. We examined male and female APOE3 and APOE4 knock-in mice across two age cohorts: young adulthood (3 months of age, eq. human ~21 years) and advanced middle age (15 months of age, eq. human ~50 years). Mice were housed with either functional voluntary running wheels or locked sedentary control wheels starting at 2 months of age. To capture the full dynamic range of diurnal resetting, we analyzed the hippocampal tissue milieu at two times of day: the conclusion of the active/wake phase and the conclusion of the restorative/sleep phase. We performed high-throughput multiplexed immunoassays to map hippocampal neuroimmune dynamics, and targeted mass spectrometry metabolomics to identify shifts in energetic demand and fuel use. In the young cohort (3 months), we found that the transition between wake and sleep is characterized by a dynamic baseline cytokine flux that is fundamentally altered by genotype, sex, and exercise condition, with young APOE4 carriers demonstrating altered kinetic profiles at the conclusion of the sleep phase following wake-phase voluntary exercise. In the aged cohort (15 months), we found shifting signatures in lipid, carboxylic acid, and amino acid metabolism pathways. Notably, sedentary APOE4 animals exhibited a pronounced metabolic deficit during the wake phase that normalized during sleep. Conversely, while voluntary exercise shifted the active-phase lipidomic profile in aged APOE4 mice, it induced selective reductions in structural and energetic metabolites by the end of the sleep cycle as compared to APOE3 counterparts. Combined, these multiomic datasets suggest that the APOE4 genotype introduces a temporal desynchrony in the brain's diurnal homeostatic regulation, altering how the hippocampus coordinates responses to metabolic demand and immune resolution between the active and restorative states. Deficits in these daily cyclical kinetics across a lifespan may represent a critical, modifiable vulnerability driving increased risk for Alzheimer's disease.

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Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.11/V3

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

Support: NIH Grant 5R01AG076625-04

Title: Neuroinflammatory effects of dietary thiamine insufficiency across ages in a 3xTg-AD mouse model of Alzheimer's Disease

Authors: *S. R. BRANNEN[1], B. BLACKBURN[2], M. HOWINGTON[3], J. PEARSON[3], S. JAHAN[2], J. ZASTRE[2];
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Abstract: Neuroinflammation is a key driver of Alzheimer's Disease (AD) progression that promotes neurodegeneration and neurotoxicity. Although thiamine (vitamin B1) insufficiency (TI) is commonly found in AD patients, most experimental models of thiamine deficiency use pyrithiamine, a thiamine antagonist that induces neurotoxicity and may not accurately reflect TI in patients. Consequences of TI include increased neuroinflammatory signaling, including expression of NLR family pyrin domain containing 3 (NLRP3) and upregulation of the transcription factor Hypoxia Inducible Factor-1 alpha (HIF-1α). Unfortunately, the contribution of TI to AD-associated neuroinflammation remains poorly defined. The objective of this work is to elucidate the contribution of dietary TI to neuroinflammation in AD. We hypothesize that dietary TI is sufficient to induce neuroinflammatory signaling and further promote AD-associated neuroinflammation in a dose-dependent manner. To test this hypothesis, female 3xTg-AD mice were treated with graded levels of dietary TI to evaluate changes in neuroinflammatory signaling. Female 3xTg-AD mice aged to twelve and eighteen months were treated with control (30 µg/day), minimum TI (1 µg/day), mild TI (0.1 µg/day), or complete thiamine deficiency (TD) (0 µg/day) diets for 14 days. Mice were treated at twelve and eighteen months of age, corresponding to earlier and later stages of amyloid and tau pathology in the 3xTG-AD model. Analysis of twelve-month-old mice treated with complete TD revealed an increase in HIF-1α expression compared to control-treated mice. Additionally, twelve-month-old mice across all treatment groups showed an increase in total Inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) expression compared to control-treated mice. Eighteen-month-old mice treated with complete TD exhibited an increase in NLRP3 expression compared with control-treated mice. Together, these findings suggest that dietary TI modulates neuroinflammatory signaling in 3xTG-AD mice, with distinct effects on NLRP3-, HIF-1α-, and IKKβ-associated pathways observed at twelve and eighteen months of age. Ongoing and future studies will continue to further define the relationship between dietary TI severity and neuroinflammatory signaling *in vivo* and will be complemented by *in vitro* experiments using mouse microglial cells to highlight the role of microglia in TI-induced neuroinflammation in AD.

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Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

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

Support: NIH R35GM146890
T32NS007453

Title: Systemic PLGA immunomodulatory nanoparticles reduce microglial activation and pathology in 5xFAD mice

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Abstract: Alzheimer’s disease (AD) is characterized by progressive cognitive decline, amyloid-β deposition, neuroinflammation, and neurodegeneration. Although myeloid cells are increasingly recognized as key contributors to disease progression, therapeutic approaches that effectively modulate neuroinflammatory responses remain limited. We investigated whether systemically administered poly(lactic-co-glycolic acid) (PLGA) immunomodulatory nanoparticles could modulate myeloid responses and improve disease-associated outcomes in the 5xFAD mouse model.
To assess cellular targeting, fluorescently labeled nanoparticles were administered intraperitoneally and particle association was evaluated in blood, spleen, and brain immune populations by flow cytometry. To test therapeutic efficacy, 6.5-month-old 5xFAD mice were treated with PLGA nanoparticles and assessed using elevated plus maze and Barnes maze testing. Brain immune composition, microglial activation, cytokine production, amyloid plaque burden, CD68 immunoreactivity, and neurodegeneration were evaluated after treatment. Male and female mice were included, behavioral and histological analyses were performed blinded to treatment group, and vehicle-treated 5xFAD and wild-type mice were used as controls.
Fluorescent nanoparticles preferentially associated with myeloid cells in the blood, spleen, and brain, with increased uptake by brain myeloid populations in 5xFAD mice compared with wild-type controls. Therapeutic treatment improved elevated plus maze behavior and partially improved Barnes maze performance. Flow cytometric analysis revealed persistent changes in brain immune composition, with the strongest effects observed in P2RY12+ microglial populations, particularly CD11c+ microglia. Treated 5xFAD mice showed reduced expression of activation and disease associated markers and decreased pro-inflammatory cytokine production whereas sustained effects in CD11b+P2RY12- infiltrating myeloid cells were more limited. Histological analysis further demonstrated reduced cortical amyloid plaque burden, decreased

CD68 immunoreactivity, and reduced neurodegeneration following treatment.
Together, these findings suggest that systemic PLGA immunomodulatory nanoparticles preferentially target myeloid populations and produce durable behavioral, immunological, and pathological benefits in 5xFAD mice. This work supports further investigation of biodegradable myeloid-targeted nanoparticles as a potential therapeutic strategy for modulating neuroinflammation in AD.

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Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

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Program #/Poster #: PSTR351.13/V5

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

Support: U54AG054345
RF1AG079125

Title: Mutation-Specific Mechanisms of Tau Pathogenesis in Humanized MAPT Gene Replacement Models: Multi-Scale Molecular, Cellular, and Structural Brain Phenotyping

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Abstract: Frontotemporal lobar degeneration with tau inclusions (FTLD-tau) encompasses genetically and clinically heterogeneous subtypes, yet most preclinical models have employed tau overexpression strategies that conflate mutation-specific biology with overexpression artifacts. To address this, the IU/JAX/PITT MODEL-AD Center generated a series of humanized MAPT gene replacement (MAPT-GR) knock-in mice bearing clinically relevant mutations, N279K, P301L, and IVS10+16, on the human H1 haplotype background, enabling physiologic expression of all six human tau isoforms with equal 3R/4R ratios. Multi-scale phenotyping at 4 and 12 months included hemi-brain bulk RNA-seq, DIA mass spectrometry proteomics, IHC-based neuronal and glial cell density quantification, tau biochemical fractionation, and in vivo T2-weighted MRI with voxel-based morphometry (VBM). Transcriptomic analyses revealed broadly AD-like and aging-aligned signatures, with the greatest number of differentially expressed genes in young N279K males, suggesting early signaling disruption prior to overt neurodegeneration. Pathway enrichment and AMP-AD module alignment demonstrated predominantly immune and metabolic alterations, with N279K and P301L models most closely

mirroring human AD biodomains, including synaptic and axonal regeneration subdomains at 12 months. Proteomic changes were widespread but showed weaker AD alignment at these timepoints, consistent with models that may be too young for strong proteomic convergence with postmortem AD. Histologically, P301L mice exhibited significant age-dependent neuronal loss by 12 months relative to H1 controls, N279K, and IVS10+16, while astrocytic responses differed across genotypes without global gliosis. Tau biochemical fractionation revealed that phosphorylation and aggregation are partially dissociable, with N279K driving early phospho-tau signaling, P301L promoting progressive insoluble and high molecular weight tau accumulation, and IVS10+16 showing intermediate phospho-tau burden. In vivo VBM of the N279K model across 4, 12, and 18 months under control and high fat diet conditions demonstrated progressive, age-dependent regional brain volume changes, with additional structural effects attributable to metabolic stress and significant sex differences in morphometric trajectories. Together, these data establish that MAPT mutations define mechanistically distinct tauopathy subtypes, diverging in transcriptomic, proteomic, cellular, biochemical, and structural brain phenotypes, and demonstrate the translational utility of the MAPT-GR platform for precision medicine approaches to tauopathy.

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Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.14/V6

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

Support: R01AG075837
LeRoy Schector Alzheimer's Re

Title: Disruption of $CD8^+$ regulatory T cell-mediated suppression of peripheral anti-Aβ autoantibody response ameliorates Alzheimer's disease in 5XFAD mice

Authors: *X. ZHANG[1], **K. JIA**[1], R. PARSONS[1], H. CANTOR[2];
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Abstract: Systemic immune tolerance may curtail the protective immune responses needed to cope with Alzheimer's disease (AD) pathology. Although disrupting CD4+ regulatory T cell (Treg)-mediated tolerance can confer protection in AD models, the contribution of a distinct CD8+ Treg subset which is programmed to inhibit the development of autoantibody responses has not yet been delineated in AD. Here we show that genetic disruption of Qa-1-restricted CD8+ Treg-dependent suppression in 5XFAD mouse model evokes a peripheral Aβ-specific autoantibody response. This response drives clearance of Aβ plaques, coupling with reduced pro-

inflammatory microglia, enhanced adult hippocampal neurogenesis (AHN), and better cognition. The improved phenotype is accompanied by expansion of T follicular helper (Tfh) cells and germinal center (GC) B cell responses, consistent with a relieved checkpoint on humoral immunity. In addition, pharmacologic destabilization of Helios+ CD8+ Tregs with the cereblon (CRBN)-dependent molecular glue degrader, DKY-709, promotes peripheral autoantibody responses and attenuates AD-related brain pathology. Together, these findings identify Qa-1-restricted CD8+ Tregs as a key immune checkpoint limiting protective humoral immunity in AD and suggest that enhancing peripheral autoantibody responses may represent a promising immunotherapeutic strategy for this disease.

Disclosures: X. Zhang: None. **K. Jia:** None. **R. Parsons:** None. **H. Cantor:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

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Program #/Poster #: PSTR351.15/V7

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

Support: Department of Defense United States of America
Cure Alzheimer's Fund
Alzheimer's Association

Title: Gamma-delta T cell-microglia crosstalk promotes CD8+ T cell infiltration and neuroinflammation in Alzheimer's disease

Authors: *A. GUIMARAES[1], R. REZENDE[2], M. OLIVEIRA[2], J. NENO[3], C. AVELAR MENDES DE VASCONCELLOS[4], T. LANSER[5];
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Abstract: Neuroinflammation is a central feature of Alzheimer’s disease (AD), contributing to neuronal injury, synaptic dysfunction, amyloid plaque accumulation, and neurofibrillary pathology. Because microglia transition from a homeostatic to a neurodegenerative phenotype in AD and promote peripheral immune-cell recruitment to the brain, we investigated whether γδ T cells regulate this process. Using male and female APP/PS1Jucker mice, APP/PS1 mice lacking γδ T cells, photoconvertible APP/PS1 mice, and single-cell RNA sequencing of peripheral blood mononuclear cells and brain samples from AD patients, we examined the timing, origin, cytokine profile, and downstream inflammatory effects of γδ T cell infiltration at 3 and 8 months of age. γδ T cells entered the brain by 3 months of age, before CD8+ T cell recruitment, and their accumulation coincided with the emergence of a neurodegenerative microglial signature (n=5/group; mean±SEM; one-way ANOVA/Tukey, $p<0.05$-0.0001). Infiltrating Vγ1 cells

predominantly produced IFN-γ, whereas Vγ4 cells secreted IL-17. At 8 months, γδ T cell deficiency improved Morris water maze performance compared with APP/PS1 controls (female n=7 APP, 15 APP/γδ−/−; male n=12 APP, 13 APP/γδ−/−; ANOVA/Tukey, p<0.01-0.0001), reduced amyloid deposition in cortex and hippocampus (n=3-4/group; Student's t test, p<0.05-0.01), shifted microglia toward a more homeostatic/phagocytic phenotype (FDR-adjusted p<0.05), and decreased CD8+ T cell infiltration (n=10/group, p<0.01-0.0001). Photoconversion experiments showed that Vγ4 γδ T cells preferentially migrated from the gut to the brain, supporting a microbiota-dependent gut-brain axis, while Vγ1 cells appeared more consistent with a lymphoid-organ origin. Human single-cell RNA sequencing further revealed enrichment of IFN-γ and IL-17 transcriptional programs in γδ T cells from AD patients, consistent with the mouse findings. Together, these results identify a pathogenic γδ T cell-microglia-CD8+ T cell axis that links peripheral immunity to neuroinflammation in AD and suggest that γδ T cells and their cytokines may represent therapeutic targets.

Disclosures: A. Guimaraes: None. **R. Rezende:** None. **M. Oliveira:** None. **J. Neno:** None. **C. Avelar Mendes de Vasconcellos:** None. **T. Lanser:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.16/V8

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

Support: This project was conducted with financial support from Allan and Company. The Stein Family Fund.

Title: Sex-Specific Relationships Between Brain Immune Signaling and Grip Strength in APP/PSEN1 Mice

Authors: *S. YOUSUF;
Radiation Oncology, Emory Univ., Atlanta, GA

Abstract: Alzheimer's disease (AD) is a multigenic and multifactorial neurodegenerative disorder driven by complex genetic and environmental etiologies. The (APP/PSEN1) transgenic mouse model closely recapitulates human AD pathology, matching over 500 differentially expressed genes moving in identical transcriptomic directions. This study investigated brain, and behavioral alterations in 7-month-old (APP/PSEN1) mice compared to age-matched wild-type (C57BL/6) controls. We evaluated cognitive performance, neuromuscular grip strength alongside brain profiles of pro-inflammatory cytokines and protein phosphorylation. Correlation analyses were performed to map the relationships between brain inflammation and behavioral outcomes. Acquisition trial performance at 3 months of age did not differ between groups; however, APP/PSEN1 mice exhibited significant deficits in reversal learning during Morris Water Maze

trials at 7 months of age compared to wild-type controls ($p < 0.05$). Grip strength did not differ significantly between wild-type and APP/PSEN1 animals. Notably, cortical M-CSF expression showed a female-specific positive correlation with grip strength ($R^2 = 0.62$, $p = 0.02$), while cortical IFNγ expression showed a male-specific positive correlation with grip strength ($R^2 = 0.71$, $p = 0.036$). Relative to age-matched wild-type C57BL/6 controls, female APP/PSEN1 mice demonstrated broadly elevated cortical cytokine expression, including increased IL-2, IP-10, RANTES, and MIP-1α levels ($p < 0.05$), a pattern not observed in male APP/PSEN1 mice. Additionally, cortical phosphorylated ERK1/2 levels were negatively correlated with grip strength in females ($R^2 = 0.57$, $p = 0.031$), but positively correlated with grip strength in males ($R^2 = 0.71$, $p = 0.036$). Together, these findings characterize sex-dependent cortical immune responses and distinct behavioral phenotypes at this critical 7-month pathological inflection point in the APP/PSEN1 model, clarifying how inflammatory and phosphoproteomic biomarkers reflect central neurodegeneration and functional impairment.

Disclosures: S. Yousuf: None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.17/V9

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

Support: CIHR Fellowship to JEH
Michael Smith Foundation for Health Research and Canadian's for Leading Edge Alzheimer's Research Fellowship to JEH
Brain Canada Grant
CIHR Grant

Title: The Inflammatory Bowel Disease microbiome worsens Alzheimer's Disease pathology in mice

Authors: *J. E. HAMDEN[1], C. SIE[2], R. ALLARAKHIA[3], G. GACE[3], C. PASCUALY[3], T. FLORKIN[4], H. LU[3], Y. LIM[3], W. BASSIOUNI FARAG[3], T. VELENOSI[3], K. ABD-ELRAHMAN[3], C. TROPINI[3], A. CIERNIA[5];
[1]Biochem. and Mol. Biol., [2]Microbiology and Immunol., [3]Univ. of British Columbia, Vancouver, BC, Canada; [4]Biochem., Univ. of Namur, Burdinne, Belgium; [5]Univ. of British Colombia, Vancouver, BC, Canada

Abstract: The intestinal microbiome and both systemic and neuroinflammation are increasingly recognized as risk factors for the development of Alzheimer’s disease (AD). Accordingly, people with inflammatory bowel disease (IBD) are at increased risk of developing AD and, on average, develop AD seven years earlier than those without IBD. The hallmark features of IBD include

altered intestinal microbiota as well as gut and systemic inflammation. Importantly, the intestinal microbiome can influence the brain through microbially produced metabolites (e.g., short-chain fatty acids) and immune signaling (e.g., microglial activation), both of which are altered in IBD and AD. However, the mechanisms that drive people with IBD to develop AD remain unknown. Here, we gavaged germ-free (GF) wild-type (WT) and 5XFAD mice with human donor samples to establish colonies of mice with healthy human control (HC) or IBD microbiomes, creating four groups: HC WT, HC 5XFAD, IBD WT, and IBD 5XFAD. Four weeks after gavage, GF WT and 5XFAD mice were bred, and subsequent generations of male and female offspring were used for all studies. We then deeply phenotyped all four groups at 2 and 6 months by assessing the intestinal microbiome (16S sequencing), brain AD and microglial pathology (immunohistochemistry, qPCR, Western blotting, flow cytometry), and serum short-chain fatty acids (liquid chromatography-tandem mass spectrometry) to better understand the mechanistic relationship between IBD and AD. Regardless of genotype, HC and IBD mice displayed vastly different microbiome compositions, and IBD mice had decreased microbial diversity compared to HC, consistent with both IBD and AD. In the brain, analysis of microglial morphology, phagocytosis, and tissue-level transcription suggested an overall shift toward a pro-inflammatory and pro-phagocytic phenotype in IBD 5XFAD mice of both sexes. Similarly, both female and male IBD 5XFAD mice exhibited increased plaque burden and increased plaque size within discrete brain regions. However, analysis of amyloid-beta processing proteins revealed sex-specific mechanisms underlying amyloid-beta pathology. Serum short-chain fatty acid analysis (propionic, butyric, and isobutyric acid) also revealed dysregulation in HC 5XFAD, IBD WT, and IBD 5XFAD mice, demonstrating a possible connection between the IBD microbiome and increased AD pathology. These data provide the first causal relationship between the IBD microbiome, serum metabolites, brain inflammation, and AD pathology in mice. Future studies will seek to determine the exact mechanisms through which IBD worsens AD and to develop therapeutic interventions.

Disclosures: J.E. Hamden: None. **C. Sie:** None. **R. Allarakhia:** None. **G. Gace:** None. **C. Pascualy:** None. **T. Florkin:** None. **H. Lu:** None. **Y. Lim:** None. **W. Bassiouni Farag:** None. **T. Velenosi:** None. **K. Abd-Elrahman:** None. **C. Tropini:** None. **A. Ciernia:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.18/V10

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

Support: NIH Grant AG074846

Title: Cell-type-specific IL-1β/IL-1R1 modulation of Aβ in Alzheimer’s Disease

Authors: *A. CRIDER[1], U. ASHERY[3], N. QUAN[2];
[1]Florida Atlantic Univ., West Palm Beach, OH; [2]Biomed. Sci., Florida Atlantic Univ., Jupiter, FL; [3]Tel Aviv Univ., Tell Aviv, Israel

Abstract: Alzheimer's disease (AD) is the most common cause of dementia and is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tau tangles. In addition to these hallmark pathologies, neuroinflammation has emerged as a critical contributor to disease progression. Pro-inflammatory signaling can facilitate Aβ clearance but may also drive neurotoxicity, whereas anti-inflammatory signaling can preserve neuronal integrity while reducing pathological protein clearance. IL-1β is of particular interest because it initiates inflammatory signaling and exhibits cell type-specific effects that may help explain this inflammatory trade-off in AD. Previous studies have examined inflammatory modulation of Aβ using supraphysiological cytokine expression and non-specific approaches. Here, we assessed Aβ-dependent changes in IL-1R1 expression to evaluate physiologically relevant, cell type-specific alterations in IL-1β signaling during AD progression and their effects on Aβ processing. We crossed an IL-1R1 reporter line and an IL-1β reporter line with the 5xFAD mouse model of AD to track these changes. We observed a plaque-related upregulation of astrocytic IL-1R1 while there was no observable difference in endothelial IL-1R1 expression. Furthermore, we found a plaque-related increase in microglial IL-1β synthesis almost exclusively at and around plaque sites. In addition, IL-1β expressing macrophages in the choroid plexus engulfed Aβ oligomers while microglia in the parenchyma did not. These results suggest that there is a special subpopulation of macrophage/microglia that engulf Aβ which is directed by IL-1β synthesis, and that astrocytic IL-1R1 signaling may be involved in the reduction of Aβ removal. Promoting cell type specific IL-1β/IL-1R1 mediated Aβ removal may offer a novel therapeutic strategy for the treatment of AD to target pathology while limiting the toxic effects of proinflammatory signaling.

Disclosures: A. Crider: None. **U. Ashery:** None. **N. Quan:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.19/V11

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

Support: NIH Grant 1R21AG070412
UND Histology Core Facility, P20GM113123
UND Histology Core Facility, U54GM128729

Title: Beta-amyloid pathology and cortical myelination is influenced by dietary allergen in App^{NL-G-F} mice

Authors: *A. E. MULLINS[1], A. BRISHTI[2], K. NAGAMOTO-COMBS[1];
[1]Biomed. Sci., Univ. of North Dakota, Grand Forks, ND; [2]Dept. of Biomed. sciences, Univ. of North Dakota, Grand Froks, ND

Abstract: Myelin is essential for effective propagation of action potentials down the axon during neuronal signaling. Although axonal demyelination and remyelination are physiological processes, pathological conditions may damage myelin or inhibit its renewal. We previously reported that the brains of C57BL/6J male mice with subclinical food hypersensitivity to a bovine whey allergen, β-lactoglobulin (BLG; Bos d 5), showed cortical demyelination with lasting neuroinflammation after continuous allergen consumption. Because long-term neuroinflammation and demyelination are shared pathologies among major neurodegenerative disorders, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease (AD), we hypothesized that prolonged allergen consumption by subclinically sensitized individuals would facilitate neurodegenerative disorders, particularly in genetically predisposed individuals. To test this hypothesis with a transgenic mouse model of AD, we subclinically sensitized 1-month-old male and female App^{NL-G-F} mice to BLG with cholera toxin as an adjuvant, placed them on a whey-protein containing diet (WP diet), and examined whether dietary allergen could accelerate and/or exacerbate the development of AD-related pathologies after 3 or 6 months of consumption of the WP diet. Because male mice developed tolerance to the allergen, as evidenced by decreased BLG-specific IgE levels, they were given a "booster" sensitization regimen every 2 weeks during WP diet exposure. We found that long-term exposure to the dietary allergen resulted in increased β-amyloid (Aβ) plaque load in the brains of BLG-sensitized mice compared to sham mice. After 3 months of the WP diet, decreased cortical levels of myelin basic protein (MBP), an essential protein for the formation of myelin, were also detected in BLG-sensitized male but not female mice. However, these levels returned to the sham level after 6 months, even with continuous WP diet. When examining the hippocampus, neither male nor female BLG-sensitized mice showed significant changes in MBP levels after exposure to the WP diet. These data suggest that BLG sensitization may affect region-specific neuronal myelination in a sex-dependent manner in early stages of AD pathology progression in genetically predisposed individuals. Further investigation of the timing of demyelination and myelin regeneration, as well as the characterization of neuroimmune responses, may define the mechanisms underlying the exacerbation of observed AD-related pathologies.

Disclosures: A.E. Mullins: None. **A. Brishti:** None. **K. Nagamoto-Combs:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.20/V12

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

Title: Differential regulation of hippocampal inflammation and antioxidant defenses in peripheral and central origin neurodegenerative models

Authors: *G. GONZÁLEZ[1], A. DIAZ[2], R. A. VAZQUEZ-ROQUE, Sr.[3], R. RODRIGUEZ PÉREZ[1], S. TREVIÑO[2];
[2]Inst. de Fisiología, [1]Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [3]Inst. de Fisiología, Benemérita Univ. Autónoma De Puebla, Puebla, Mexico

Abstract: Neurodegenerative disorders are driven by complex interactions between chronic inflammation and oxidative stress; however, the mechanisms through which peripheral metabolic dysfunction and central amyloidogenic insults affect hippocampal homeostasis remain poorly understood. In this study, we evaluated hippocampal inflammatory and redox profiles in male Wistar rats subjected to two distinct neurodegenerative models: metabolic syndrome (MetS) induced by a high carbohydrate diet and central neurodegeneration induced by intrahippocampal amyloid-β (Aβ) administration. MetS induced a pronounced disruption of hippocampal redox homeostasis, characterized by a severe impairment of the glutathione antioxidant system. Total glutathione, reduced glutathione (GSH), glutathione peroxidase (GPx), glutathione-S-transferase (GST), and glutathione reductase (GR) activities were significantly decreased, indicating a loss of antioxidant capacity and suggesting a state of functional exhaustion of redox defenses. These alterations were accompanied by inflammatory changes consistent with a chronic low-grade neuroinflammatory environment. In contrast, Aβ administration triggered a robust hippocampal inflammatory response, evidenced by elevated levels of IL-1β, IL-6, TNF-α, and IL-17. Remarkably, this pro-inflammatory profile was paralleled by significant increases in IL-10, TGF-β, and IL-1 receptor antagonist (IL-1Ra), indicating the simultaneous activation of endogenous immunoregulatory pathways. At the redox level, Aβ-treated animals exhibited increased catalase activity, elevated total glutathione and oxidized glutathione (GSSG) concentrations, and selective modulation of glutathione-dependent enzymes. Despite evidence of oxidative challenge, lipid peroxidation and nitrosative damage remained largely controlled, suggesting the establishment of compensatory antioxidant mechanisms. Taken together, these findings reveal that peripheral and central neurodegenerative insults induce distinct hippocampal phenotypes. Whereas MetS promotes progressive failure of antioxidant defenses and redox imbalance, Aβ exposure elicits a coordinated inflammatory and antioxidant adaptive response that partially preserves hippocampal homeostasis. These results support the existence of stimulus-specific regulatory programs that may critically influence the onset and progression of neurodegenerative processes.

Disclosures: G. González: None. **A. Diaz:** None. **R.A. Vazquez-Roque:** None. **R. Rodriguez Pérez:** None. **S. Treviño:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.21/V13

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

Support: AHA 24 TPA1304527
AHA 25 TPA1481771

Title: Alcohol Exposure Accelerates Alzheimer's Disease-Like Brain Injury in 3xTgAD Mice by Disrupting Glymphatic and Meningeal Lymphatic Clearance

Authors: B. SATYAVOLU[1], S. REDDY[2], ***N. TYAGI**[1];
[2]Physiol., [1]Univ. of Louisville, Louisville, KY

Abstract: Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory loss, amyloid accumulation, tau pathology, synaptic dysfunction, neuroinflammation, and neuronal injury. Alcohol exposure is increasingly recognized as an environmental risk factor that may worsen neurodegenerative processes by promoting oxidative stress, inflammatory signaling, and cellular damage. In this study, we investigated the effect of alcohol on brain damage in 3xTg-AD mice, a well-established model that develops both amyloid and tau pathology. In this study, whether alcohol worsens AD progression by disrupting brain waste-clearance pathways, including glymphatic function and meningeal lymphatic drainage, which may reduce the clearance of amyloid, tau, and inflammatory mediators from the brain.Age-matched wild-type and 3xTg-AD mice were treated with alcohol, followed by behavioral, biochemical, molecular, and histological analyses. Alcohol-treated 3xTg-AD mice showed greater cognitive and memory impairment compared with wild type wild-type controls including deficits in learning, spatial recognition, and working memory. Brain tissue analysis revealed increased neuronal injury, enhanced glial activation, elevated pro-inflammatory signaling, and increased oxidative stress. Importantly, alcohol exposure may impair glymphatic clearance by altering aquaporin-4 polarization, astrocyte function, vascular integrity, and cerebrospinal fluid-interstitial fluid exchange. Reduced clearance capacity could promote accumulation of toxic amyloid and tau species, enhance neuroinflammation, and accelerate synaptic and neuronal loss. Overall, this study proposes that alcohol exposure aggravates Alzheimer's disease-like brain damage in 3xTg-AD mice by impairing brain clearance mechanisms in addition to promoting inflammation and oxidative injury. This novel concept highlights the glymphatic-meningeal lymphatic system as a potentially important and underexplored pathway linking alcohol exposure to accelerated AD progression.

Disclosures: B. Satyavolu: None. **S. Reddy:** None. **N. Tyagi:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.22/V14

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

Support: U01 Grant AG088113

Title: A prophylactic treatment with a novel EP2 antagonist TG11-283 attenuates neuroinflammation in the 5xFAD mouse model of Alzheimer's disease

Authors: H. XING, ***S. KAUR**, W. WANG, N. H. VARVEL, T. GANESH;
Dept. of Pharmacol. and Chem. Biol., Emory Univ., Atlanta, GA

Abstract: Motivation Neuroinflammation is a consistent pathological feature of Alzheimer's disease (AD). Recent studies suggest that EP2 receptor activation exacerbates neuroinflammatory signaling in aging and AD models. We previously reported that EP2 antagonism quenches brain inflammation during the prodromal stage in 5xFAD female mice on a C57BL/6J (B6) background and in male mice on a mixed B6-SJL background. To test whether EP2 antagonism is protective at early disease onset, we evaluated a novel, potent, brain-penetrant EP2 antagonist in 5xFAD mice on the B6 background. **Methods** Male and female 5xFAD (JAX 034848) mice and non-transgenic littermate controls (n=15/group/sex) were used to evaluate prophylactic TG11-283 efficacy. At 5 months of age, mice received TG11-283 (0, 22, or 66 mg/kg/day) in drinking water for 3 months. Cohorts were sex-balanced, body weight was monitored throughout treatment, and all treatment administration and experimental procedures were conducted blinded. Brain tissues were analyzed by IHC to quantify microgliosis and astrogliosis using Iba1+ and GFAP+ staining. Cortical samples were further analyzed by proteomics, NULISA, qRT-PCR, Western blotting, and ELISA. **Results** TG11-283 was well tolerated, with no adverse effects on body weight. Treatment reduced gliosis across CA1, CA2, CA3, dentate gyrus, striatum, parietal cortex, and temporal cortex. In females, microgliosis and astrogliosis were reduced by 55.32 ± 11.06% to 71.44 ± 10.06% (n=15), and in males by 38.26 ± 10.01% to 56.66 ± 6.8% (n=14; two-way ANOVA). qRT-PCR showed downregulation of S100b and CD11b, with an approximately 30% reduction in glial signature score in males (n=15; unpaired t-test). Western blotting confirmed reduced GFAP in female cortex (n=6, p=0.0106; unpaired t-test). Proteomics revealed reductions in TREM2, GFAP, GSDMD, amyloid-β40, and APOE while Iba1 and YKL-40 were not significant after FDR correction (p=0.00000356 and p=0.000981 before FDR adjustment). ELISA showed a 31.1% reduction in soluble Aβ42 in treated female mice (n=15; unpaired t-test), and western blotting showed decreased APP and C-terminal fragments (n=6; unpaired t-test). EP2 antagonism also suppressed COX1 (p=0.0099), COX2 (p=0.0357), and pNF-κB (p=0.0096). NULISAseq showed normalization of CCL2, CCL4, SNAP25, S100b, GPNMB, and IL-33 with 25/34 dysregulated proteins shifted toward baseline. **Conclusion** TG11-283 was tolerated, with no adverse effects on body weight. It suppressed neuroinflammation, gliosis, amyloid pathology, and inflammatory signaling, supporting EP2 antagonism as a promising disease-modifying strategy for AD.
H. Xing, S. Kaur contributed equally.

Disclosures: H. Xing: None. **S. Kaur:** None. **W. Wang:** None. **N.H. Varvel:** None. **T. Ganesh:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

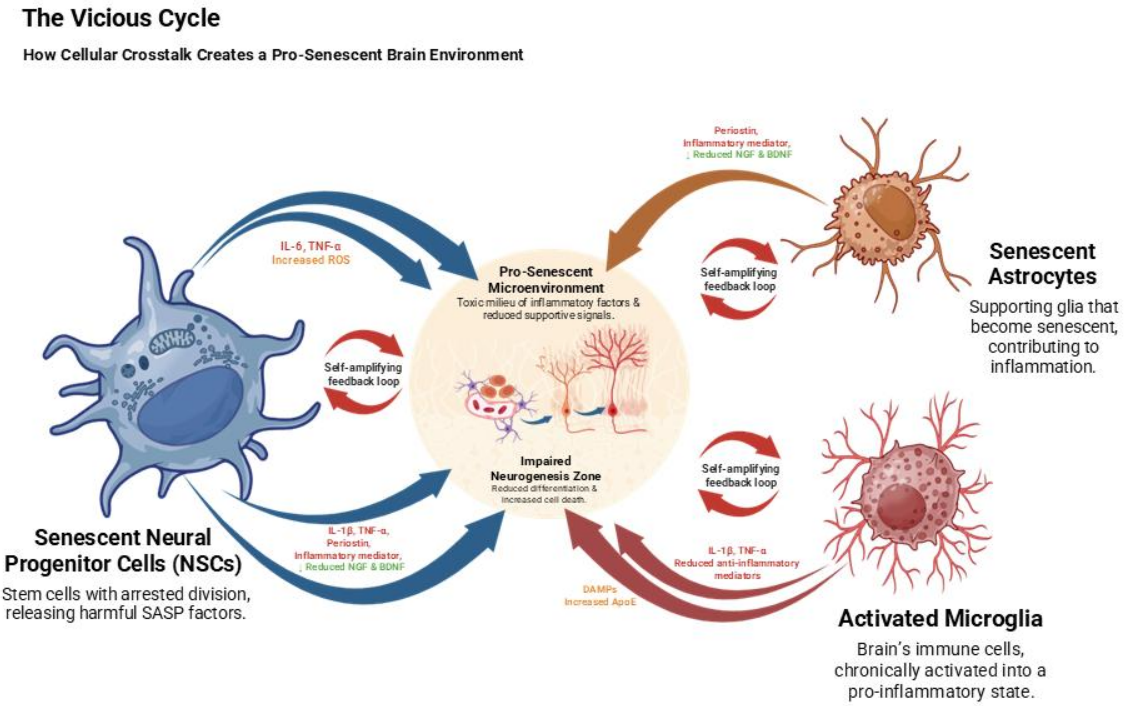
Program #/Poster #: PSTR351.23/V15

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

Title: SG001 Reverses Senescence-Associated Impairment of Adult Neurogenesis in the Aging APP/PS1 Brain

Authors: *M. MITTAL[1], S. GUPTA[2];
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Abstract: Adult neurogenesis progressively declines in Alzheimer's disease, but the role of senescence-linked neuroinflammation in this process remains unclear. We utilized a combination of immunohistochemical markers in APP/PS1 mice aged 6 to 18 months (n=6) to examine age-dependent changes in neural progenitor activity and neural senescence in the dentate gyrus region of the hippocampus, specifically evaluating the impact of inflammation on adult neurogenesis. In addition to staining for neuronal nuclei (NeuN) protein, which identifies all neurons and a decrease would indicate neurodegeneration, we examined doublecortin (DCX), Sox2, and Ki67 expression, which are primarily expressed during neurogenesis, along with the senescence marker p21, which indicates increased cellular senescence. We also measured glial fibrillary acidic protein (GFAP) and Iba1 levels; an increase in these markers reflects elevated astrocytic and microglial activation, respectively.
Our findings indicate that with advancing age, hippocampal neurogenesis declines, evidenced by reduced DCX and Ki67 expression, alongside increased p21 levels, indicating enhanced cellular senescence. These changes are accompanied by heightened glial activation, as reflected by elevated GFAP and Iba1 levels. Conversely, treatment with SG001, a lab-patented small-molecule drug that enhances a selective endoplasmic reticulum autophagy, and as a result of which increased DCX- and Ki67-positive cells, reduced p21 expression, and decreased GFAP levels. This suggests a restoration of progenitor activity and a mitigation of the senescent inflammatory environment.
These results demonstrate that the loss of neuronal connectivity in the Alzheimer's mouse model is associated with reduced neurogenic capacity and increased senescence. Moreover, SG001 appears to partially reverse these defects. These results support a model in which targeting senescence-associated glial dysfunction may help preserve neural progenitor function and improve regenerative potential in Alzheimer's disease.



Disclosures: M. Mittal: None. **S. Gupta:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.24/V16

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

Title: CCL3-CCR1 Axis Drives Neutrophil Infiltration and NET Formation to Promote Amyloid Pathology and Cognitive Decline in Alzheimer's Disease

Authors: *S. WANG;
Sch. of Med., Tongji university, shanghai, China

Abstract: Purpose: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by Aβ plaque accumulation, synaptic loss, and cognitive decline. Neuroinflammation is a central driver of AD pathology; however, the contribution of peripheral

immune infiltration, particularly neutrophils, and the chemokine signals governing their brain recruitment remain poorly understood. This study aimed to characterize the role of CCL3-CCR1 signaling in mediating neutrophil infiltration into the AD brain and to elucidate the underlying mechanisms. **Methods:** The expression and spatial distribution of CCL3 and CCR1 were profiled by Western blotting, ELISA, scRNA-seq and immunofluorescence. Neutrophil infiltration and NET formation were interrogated through flow cytometry, immunofluorescence, and scRNA-seq-based subpopulation dissection. Cognitive function was assessed via Y-maze, Morris water maze, and fear conditioning. Complementary genetic and pharmacological strategies, encompassing Ccl3 knockout, CCL3-neutralizing antibody delivery, and systemic CCR1 inhibition, were deployed to delineate mechanistic contributions in vivo and in vitro. **Results:** CCL3 and its receptor CCR1 were markedly upregulated in AD mouse brains and human AD tissue, with CCL3 predominantly localized to plaque-associated microglia and CCR1 enriched in infiltrating neutrophils. CCL3-CCR1 activation promoted peripheral neutrophil recruitment into the AD brain, where neutrophils acquired a highly activated, NET-forming phenotype. NET-associated neutrophil elastase (NE) accumulated around Aβ plaques and contributed to enhanced amyloid pathology. Single-cell transcriptomic analysis revealed a marked enrichment of CD177+ activated neutrophils in AD mouse brains, corroborated by peripheral blood transcriptomic profiling in AD patients. Ccl3 knockout significantly reduced neutrophil infiltration, attenuated amyloid burden and synaptic injury, and improved cognitive performance. Similarly, hippocampal CCL3-neutralizing antibody delivery or systemic CCR1 inhibition effectively suppressed neutrophil accumulation and rescued cognitive deficits. **Conclusion:** This study demonstrates that CCL3-CCR1 signaling drives pathological neutrophil infiltration and NET formation in the AD brain, linking microglial activation to peripheral immune recruitment and amyloid pathology. Targeting this axis via CCL3 neutralization or CCR1 inhibition attenuated neuroinflammation and rescued cognitive function, establishing CCL3-CCR1 as a promising therapeutic target for AD.

Disclosures: S. wang: None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.25/V17

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

Title: Characterization of AAV9-A53T α-Syn induced Synucleinopathy and Spontaneous Amyloidopathy in Brains of Aged Nonhuman Primates

Authors: *L. YANG, G. WANG, Y. ZHAO, R. PEREZ, Y. XU, S. ZHA;
Kunming Biomed Intl., Kunming, China

Abstract: Small animal models of Parkinson's (PD) and Alzheimer's disease (AD) lack translational validity due to significant genetic and physiological disparities from humans. Developing non-human primate (NHP) models is urgently needed for translational research. We characterized a novel PD model via stereotaxic delivery of AAV9-A53T α-Syn to the substantia nigra of aging monkeys, comparing dopaminergic degeneration to the traditional MPTP model. Additionally, we identified spontaneous-onset amyloidopathy in aged monkeys, analyzed Aβ42/Aβ40 biomarkers, and evaluated a therapeutic intervention in PET-Aβ positive subjects. Twenty monkeys (22-28 years) received unilateral AAV9-A53T α-Syn injections and were observed for two years. [18F-FP-(+)-DTBZ] PET/CT revealed progressive dopaminergic signaling decline in the injected putamen and caudate (SUVR 7.5 at year one, 6.0 at year two) versus the intact side (SUVR 8.5). CSF analysis showed increasing homovanillic acid (HVA) during degeneration, while tyrosine hydroxylase immunostaining confirmed dopaminergic neuron loss on the injected side. Unilateral MPTP delivery (2 mg/kg, carotid artery) caused significant dopaminergic depletion in the injected hemisphere by day 7. By week 4, the contralateral side was also affected. Unlike the AAV model, CSF HVA decreased 4 weeks post-MPTP. Screening 150 aged animals (20-28 years) via 18F-florbetapir PET/CT revealed ~50% exhibited cortical and hippocampal amyloidopathy (SUVR 1.2-2.5), confirmed by histopathology. CSF MSD/ELISA analysis showed significant decreases in Aβ42, Aβ40, and Aβ42/Aβ40 compared with young adults; however, similar decreases occurred in age-matched amyloidopathy-negative monkeys. A 6-week therapeutic intervention in 6 amyloidopathy monkeys significantly reduced brain Aβ deposition on PET/CT (SUVR from 1.6 to 0.8). Overall, we present validated AAV9-A53T α-Syn NHP PD and spontaneous-onset NHP AD models. Supported by PET/CT, biomarkers, and histopathology, these offer valuable preclinical platforms for testing neurodegenerative therapeutics.

Disclosures: L. Yang: None. **G. Wang:** None. **Y. Zhao:** None. **R. Perez:** None. **Y. Xu:** None. **S. Zha:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.26/V18

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

Title: Chronic estradiol exposure elevates the markers of nitrosative stress and neuroinflammation in brainstem noradrenergic nuclei

Authors: *A. MURUGAN[1], A. PALANIYAPPAN[2], Y.-J. CHUANG[2], S. M. MOHANKUMAR[3], P. S. MOHANKUMAR[4];
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Abstract: The brainstem noradrenergic nuclei, including the locus coeruleus (A6), nucleus tractus solitarius (A2), and ventrolateral medulla (A1), regulate cognitive, autonomic, and neurovascular functions and are vulnerable to age-related neurodegenerative changes. Although estradiol (E2) has been reported to exert neuroprotective effects, the consequences of prolonged estrogen exposure on inflammatory signaling within these nuclei remain unclear. We investigated the effects of chronic E2 exposure on nitrate and interleukin-1β (IL-1β) levels in female rats. Young Sprague Dawley rats (3-4 months) were either sham-implanted or implanted with 17β-estradiol (20 ng/day) slow-release pellets for 30 days (E-30), 60 days (E-60) or 90 days (E-90), and old constant-estrous (OCE) animals (16-18 months) were included as a model of prolonged endogenous estrogen exposure. Nitrate levels, an index of nitric oxide production, and interleukin-1β (IL-1β) expression were quantified in A1, A2, and A6 brainstem nuclei. Chronic E2 exposure increased nitrate concentrations in A6 nucleus following 90 days of exposure and in OCE animals across all three nuclei. Similarly, IL-1β expression was elevated in A1, A2, and A6 following chronic E2 treatment, with significant increases observed after 90 days of exposure and in OCE animals. The molecular and cellular changes associated with these findings are currently under investigation. These findings demonstrate that prolonged estrogen exposure promotes neuroinflammatory and nitrosative stress responses in brainstem noradrenergic nuclei. Given the early vulnerability of these nuclei in Alzheimer's disease, these findings suggest a potential mechanism by which prolonged estrogen exposure may influence female susceptibility to neurodegeneration.

Disclosures: A. Murugan: None. **A. Palaniyappan:** None. **Y. Chuang:** None. **S.M. Mohankumar:** None. **P.S. Mohankumar:** None.

Poster

PSTR351: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vivo* Models II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.27/V19

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

Support: NIH R21EB034494

Title: A Bioluminescent Kinase Sensor (BlinKS) Platform for Noninvasive Detection and Modulation of Neuroinflammation in Aging-Associated Neurodegeneration

Authors: *O. DUBEY[1], N. SIMON[2], M. CHATTERTON[2], J. BAKKE[1], J. ROSSIGNOL[3], E. D. PETERSEN[4];
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Abstract: Chronic inflammation contributes to numerous pathological conditions, including neurodegenerative diseases such as Alzheimer's disease and related dementias. In the central

nervous system, sustained inflammatory signaling drives disease progression, yet current anti-inflammatory therapies often lack cellular specificity and can cause systemic side effects. To address these limitations, we are developing a genetically encoded Bioluminescent Kinase Sensor (BlinKS) platform for real-time detection and regulation of inflammatory signaling. BlinKS detects activation of key inflammatory pathways, including JAK/STAT and NF-κB, and converts kinase activity into a bioluminescent output. The sensor consists of a split luciferase reconstituted through phosphorylation-dependent interactions between a phospho-amino acid binding domain (PAABD) and pathway-specific kinase substrates. We have generated and validated BlinKS variants targeting JAK1, JAK2, STAT1, STAT3, and candidate NF-κB pathway kinases, demonstrating pathway-responsive bioluminescent signals in cell-based assays.To improve sensitivity and dynamic range, we are optimizing luciferase variants, linker architecture, and PAABD-substrate pairings while expanding the repertoire of inflammatory kinase targets. In addition, BlinKS-generated bioluminescence can activate EL222-based optogenetic circuits, enabling expression of downstream anti-inflammatory genes such as IL-10. To assess in vivo utility, we are applying BlinKS in aged GFAP-IL6 transgenic mice, a model of chronic neuroinflammation relevant to aging-associated neurodegeneration. Longitudinal bioluminescence imaging enables noninvasive monitoring of inflammatory kinase activity and provides a platform for evaluating therapeutic modulation of neuroinflammatory signaling. Collectively, these studies establish BlinKS as a versatile tool for monitoring inflammation and lay the foundation for precision approaches to studying and treating neuroinflammatory and neurodegenerative disorders.

Disclosures: O. Dubey: None. **N. Simon:** None. **M. Chatterton:** None. **J. bakke:** None. **J. Rossignol:** None. **E.D. Petersen:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.01/V20

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

Title: Altered Alpha Dynamics in Alzheimer’s Disease: Evidence from Eyes-Open and Eyes-Closed Resting-State EEG

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Abstract: ***Objective:*** To test whether eyes-open (EO) and eyes-closed (EC) resting EEG distinguish controls, asymptomatic Alzheimer’s disease (AAD), and Alzheimer’s disease (AD), and reveal altered alpha modulation.***Background***: AD biomarkers from amyloid/tau PET, CSF, plasma, and structural imaging provide diagnostic information but limited insight into dynamic cortical function. Resting EEG may complement these biomarkers by capturing synaptic and

network-level dysfunction. Prior studies identify AD-related EEG slowing, including reduced alpha activity, slower individual alpha frequency, and increased theta/alpha balance. However, most analyses focus on a single resting condition or combine EO and EC recordings. Whether EO and EC EEG provide complementary markers, and whether alpha modulation is impaired in AD or altered in AAD, remains unclear.***Methods***: We analyzed continuous resting EEG from 45 control, 6 AAD, and 29 AD observations. EO and EC recordings were analyzed separately without ERP procedures. Welch spectra were used to extract delta, theta, alpha, and beta features, emphasizing global, posterior, and occipital alpha power, alpha peak frequency, and theta/alpha ratio. For paired observations, EC-minus-EO alpha attenuation and alpha log-ratio features were computed. Group differences used Kruskal-Wallis tests, Mann-Whitney U tests, and Cliff's delta.***Results***: AD showed consistent spectral slowing. In EC rest, AD had reduced alpha power, slower global alpha peak frequency, and elevated posterior/global theta-alpha ratios compared with controls. In EO rest, AD showed elevated occipital, posterior, and global theta-alpha ratios, reduced occipital alpha relative power, and lower posterior alpha peak frequency. Paired analysis showed reduced alpha modulation in AD, including lower occipital/posterior alpha attenuation (KW $p=0.0098/0.0112$; Control vs AD $p=0.0023$; $d=0.429$ for both). Exploratory AAD analyses showed significant differences from AD, including higher EC global alpha peak frequency ($p=0.0039$; $d=0.75$), higher EC occipital alpha relative power ($p<0.001$; $\delta=0.84$), and lower EO occipital/posterior/global theta-alpha ratios (all $p<0.001$; $d=-1.0$). AAD also had lower EO posterior and global theta-alpha ratios than controls ($p=0.0046$ and $p=0.0014$), suggesting a distinct EEG profile.***Conclusion***: EO and EC resting EEG revealed AD-related spectral slowing and reduced alpha modulation. AAD Pilot data suggest a distinct EEG profile in the presymptomatic stage. These findings support resting-state EEG as a complementary functional biomarker that captures dynamic neural dysfunction beyond conventional AD biomarkers.

Disclosures: T. Tran: None. **R. Fernandez Romero:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.02/V21

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

Title: Spatial Mapping of Epichaperome Remodeling in Human Prefrontal Cortex Across the Alzheimer's Disease Continuum

Authors: *S. BAY[1], A. RODINA[3], F. HAUT[5], T. ROYCHOWDHURY[2], E. K. ARGYROUSI[6], A. STANISZEWSKI[7], S. SHARMA[3], S. CHAKRABARTY[9], C. DIGWAL[3], A. STANISAVLJEVIC[10], A. LABUZA[13], M. J. ALLDRED[11], P. PANCHAL[3], E. ROSIEK[3], H. SASAGURI[14], T. C. SAIDO[15], J. SCHNEIDER[16], D. A. BENNETT[17], P. E. FRASER[18], H. ERDJUMENT-BROMAGE[19], T. A. NEUBERT[20], S. D. GINSBERG[12], O. ARANCIO[8], G. CHIOSIS[4];

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Abstract: Selective vulnerability of specific neuronal populations and cortical layers is a defining feature of Alzheimer's disease (AD), yet the molecular events that mark vulnerable cells during disease progression remain incompletely understood. Epichaperomes are stable, disease-associated assemblies of chaperones and co-chaperones that remodel protein interaction networks and have been linked to proteome dysfunction, synaptic failure, and cognitive decline in AD. Because these assemblies report interaction-state remodeling rather than changes in gene expression or protein abundance alone, they provide a potential molecular readout of cellular dysfunction in vulnerable brain regions.Here, we mapped the spatial and cell-type distribution of epichaperomes in postmortem dorsolateral prefrontal cortex (Brodmann area 9; BA9) from individuals spanning no cognitive impairment (NCI), mild cognitive impairment (MCI), and AD. We combined multiplex immunofluorescence with an epichaperome-selective chemical biology probe to visualize epichaperome assemblies together with neuronal, astrocytic, and nuclear markers. This approach enabled anatomical localization of epichaperome-positive cells across cortical layers and disease stages.Epichaperome signal was largely absent or minimal in NCI cortex but became prominent in MCI and AD, with distinct laminar and cell-type-associated patterns. Epichaperome-positive cells were detected in neuronal and astrocytic compartments within vulnerable cortical regions, supporting the idea that interaction-state remodeling marks specific cellular populations during the AD continuum. As disease severity increased, epichaperome remodeling became more extensive and was associated with greater disruption of cortical organization.These findings define a spatial map of epichaperome remodeling in human AD cortex and identify cellular populations vulnerable to interaction-state pathology.

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Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

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Program #/Poster #: PSTR352.03/V22

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

Support: NSF Cooperative Agreement DMR-1644779
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NIA R01 AG070094
NIMH R56 MH133929

Title: Longitudinal Structural MRI of TgF344-AD Model of Alzheimer's Disease Demonstrates Early Changes in Hippocampal Formation

Authors: *J. RADOVICH[1], K. HARDIN[2], S. RAGSDALE[3], J. OGG[2], A. A. WILBER[2]; [1]Chem. and Biomed. Engin., [2]Psychology, Florida State Univ., Tallahassee, FL; [3]Univ. of Arizona, Tucson, AZ

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disorder affecting millions. Despite extensive research, a critical gap remains in understanding early indicators of AD, because early data points are often absent in AD animal models. We aim to address this deficiency by collecting longitudinal data from 2-18mo rats. Longitudinal *in vivo* MRI data were obtained from female double transgenic TgF344-AD rats and their littermate controls (WT) at 21.1T to evaluate structural connectivity. Under 1-3% isoflurane, whole brain spin-echo EPI DTI images were acquired (200x200x1000μm, 18 directions, b=1000 s/mm²). Imaging was conducted at 2, 4, 6, 10, 12, 16, & 18mo of age (N≈8/age/phenotype). Data processing included motion and eddy current correction, skull stripping, and atlas-based ROIs (Fischer 344 atlas) on diffusion tensor metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), and radial diffusivity (RD). Genotype blinding was maintained throughout. Preliminary results indicate that brain microstructure is dynamically altered with age in many ROIs, with the most notable changes being in the hippocampal formation. Tensor metric AxD, a measure for diffusivity parallel to the neuronal axes, increases in AD rats from 2-4mo then decreases at 6mo, while it continues to increase in WT. MD increases at 6mo in TgF344-AD rats and continues increasing with age. The FA, which measures the degree of directional water diffusion, of white matter tracts (corpus callosum and fornix) start decreasing around 6 and 10mo. Interestingly, place/action spatial learning and memory deficits emerge at 6mo, after changes in structure have emerged. These metrics demonstrate impacts in structural connections when little amyloid aggregation should have occurred. WT rats also have changes with age and patterns are similar, but occur much later, beginning around 12mo as expected for normal aging. Resting state-fMRI was conducted simultaneously and is currently being assessed to understand the functional consequences of these structural changes. This data covers the gap in early longitudinal microstructural brain alterations in a popular transgenic AD model. It demonstrates potentially critical information about how the disease impacts the brain earlier than previously recognized which may allow for earlier intervention points/markers. The increase and then decrease in structural connectivity could relate to period of early hyperactivity followed by hypoactivity as

seen in TgF344-AD rats, other rodents, and AD patients (Tudela et al, 2019; Waegenaere et al, 2024; Sperling et al, 2010), a possibility we are directly assessing with our fMRI data.

Disclosures: J. Radovich: None. **K. Hardin:** None. **S. Ragsdale:** None. **J. Ogg:** None. **A.A. Wilber:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

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Program #/Poster #: PSTR352.04/Web Only

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

Support: BK21 FOUR, Korean Southeast Center for the 4th Industrial Revolution Leader Education
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Title: White Matter Integrity Is Associated With Instrumental Activities of Daily Living Across the Alzheimer's Disease Continuum: A Diffusion MRI Study

Authors: *K. BAEK[1], G. JEON[1], J. JEONG[1], Y.-M. LEE[2], H.-W. SHIM[2];
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Abstract: Instrumental activities of daily living (IADL) refer to an ability to perform complex everyday tasks (e.g., cooking, financial management) and tend to decline progressively along the Alzheimer's disease (AD) continuum. Previous studies have shown significant associations of IADL with cognition, cerebral atrophy, and white matter hyperintensities. However, whether WM microstructural changes contribute to IADL decline beyond global cognitive impairment remains unclear. Using diffusion tensor imaging (DTI), this study examined fractional anisotropy (FA) and mean diffusivity (MD) across 50 atlas-defined WM regions in 743 participants spanning the AD continuum: subjective cognitive decline (n = 179), mild cognitive impairment (n = 398), and AD dementia (n = 166). Multiple linear regression analyses examined relationships between regional DTI metrics and S-IADL or MMSE-DS scores, adjusting for demographics and brain tissue volumes. In hierarchical regression models, demographics and tissue volumes were entered first, followed by MMSE-DS scores, and finally DTI metrics to test their additional explanatory value for S-IADL. Lower FA and higher MD in widespread WM tracts, including the corpus callosum and anterior corona radiata, were associated with poorer IADL performance and lower MMSE-DS scores. Several regions showed IADL associations independent of global cognition, and inclusion of DTI metrics significantly increased explained variance (baseline $R^2 = 0.375$; $\Delta R^2 = 0.037$). These findings suggest that microstructural WM degeneration, particularly in the corpus callosum and anterior corona radiata, independently

contributes to functional decline across the AD continuum. Incorporating WM integrity markers with cognitive and volumetric measures may improve early detection and prediction of IADL deterioration in individuals at risk for or along the course of AD.

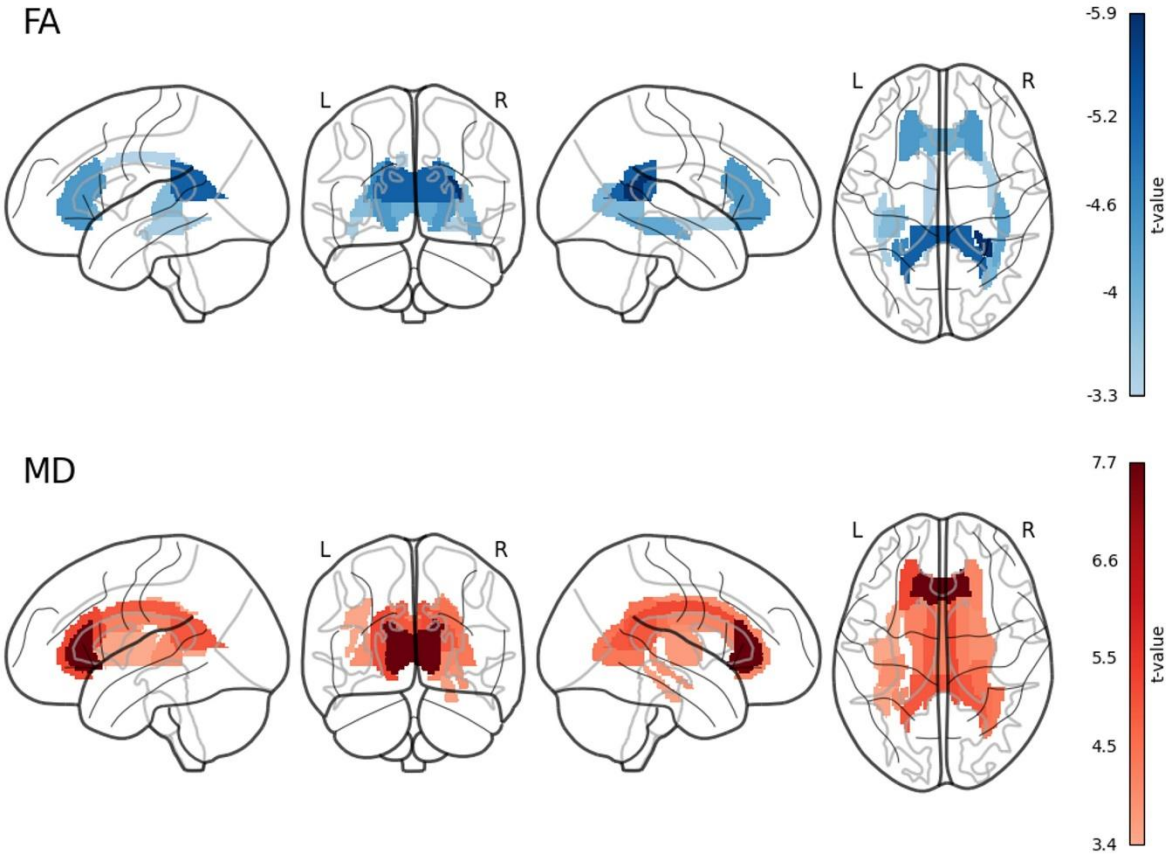


Figure 1. White matter ROIs showing fractional anisotropy (FA) or mean diffusivity (MD) significantly associated with IADL. ROIs were considered significant at $p < 0.05$ after correction for multiple comparisons (Bonferroni correction), adjusting for age, sex, years of education, gray matter volume, and white matter volume. Each ROI was color-coded according to its t-value. Negative correlations are shown in blue and positive correlations in red.

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Poster

PSTR352: Alzheimer's Disease: Imaging

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Program #/Poster #: PSTR352.05/V23

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

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AMED JP24zf0127012
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MEXT Project JPMXS04504002

Title: An in vivo MRI-based whole-brain morphometric analysis framework: Validation in a tauopathy mouse model with brain atrophy

Authors: *R. KOIKE[1], A. SUMIYOSHI[2], S. UCHIDA[1], M. SHIMOJO[1], T. MINAMIMOTO[1], M. HIGUCHI[1,3], H. MIZUMA[1,3];
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Abstract: *In vivo* imaging, including magnetic resonance imaging (MRI), is a powerful translational tool for the longitudinal assessment of brain atrophy and therapeutic responses in both preclinical and clinical settings. However, accurate whole-brain volumetric analysis in living mouse models remains challenging, particularly in models exhibiting severe neurodegeneration and marked anatomical alterations. To address this challenge, we established an *in vivo* MRI-based analysis framework comprising two complementary segmentation strategies: atlas-based and intensity-based segmentation. To construct this framework, we analyzed longitudinal *in vivo* MRI data acquired at 3 and 6 months of age from rTg4510 mice, which overexpress mutant human tau and exhibit age-dependent tau pathology and brain atrophy, together with age-matched control mice. We first implemented an atlas-based segmentation strategy for longitudinal regional volumetric analysis. Using MRI data acquired from rTg4510 and control mice, we constructed an average anatomical template and a corresponding brain atlas. Deformation-based propagation of the atlas to individual MR images enabled whole-brain ROI segmentation and regional volumetric quantification. Because heterogeneous brain atrophy in rTg4510 mice reduced the reliability of spatially regularized segmentation, we next developed an intensity-based segmentation strategy that minimized dependence on spatial information. A log-scaled T1w/T2w ratio enabled intensity-based classification of gray matter-like, white matter-like, and cerebrospinal fluid-like tissues even in the presence of brain atrophy, resulting in quantification of global tissue volume changes and voxel-based morphometric analysis. Using these complementary strategies, we identified region-specific patterns of age-dependent volumetric change during disease progression in rTg4510 mice. Together, this framework facilitates the preclinical evaluation of therapeutic interventions targeting tau-related neurodegeneration. Furthermore, it may serve as a standardized platform for *in vivo* MRI-based morphometric analysis in a wide range of mouse models, including those exhibiting brain morphological changes associated with other neurological disorders, brain development, and aging.

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Poster

PSTR352: Alzheimer's Disease: Imaging

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.06/V24

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

Support: JSPS KAKENHI Grant JP24K02357

Title: In vivo assessment of progressive tau pathology and neurodegeneration of rTg4510 mouse model for tauopathy in C57BL/6J genetic background

Authors: *Y. NOMURA[1,2], R. YANAI[2], T. MINAMIHISAMATSU[2], C. SEKI[2], H. MIZUMA[2,3], R. KOIKE[2], S. UCHIDA[2], M. HIGUCHI[2,3,4], M. SHIMOJO[2,4], H. MISAWA[1], N. SAHARA[5,2,6];
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Abstract: Intracellular accumulation of tau protein associated with progressive neuronal loss is a pathological hallmark of tauopathies, including Alzheimer’s disease. Although genetically engineered mouse models that recapitulate human tau pathology provide valuable insights into disease mechanisms, their pathological phenotypes are often influenced by genetic background, gender, and environmental conditions. We previously established rTg4510 mice on a C57BL/6J genetic background(B6-rTg4510) and reported that this background conversion attenuates pathological phenotypes observed in rTg4510 mice with the original FVB/129-rTg4510 mice. To further characterize disease progression in this model, we performed longitudinal tauPET and MRI analyses to evaluate the spatiotemporal progression of tau pathology and neurodegeneration in B6rTg4510 mice. TauPET imaging using [^{18}F]florzolotau (also known as [^{18}F]APN1607 and [^{18}F]PMPBB3), a tracer that selectively binds βsheetrich aggregated tau, showed little increase in radioactive signal relative to controls at 3 months of age, but gradually increased by 10 months of age. This increase was accompanied by progressive brain atrophy detected by MRI. Notably, compared with the original FVB/129rTg4510 mice, B6-rTg4510 mice exhibited a markedly slower rate of pathological progression. Consistent with these in vivo findings, postmortem biochemical and immunohistochemical analyses demonstrated progressive tau accumulation and neuronal loss in both FVB/129 and B6 rTg4510 mice. These findings support the utility of PET-based assessments for tracking tau pathology throughout the progression of neurodegenerative tauopathies. Our findings indicate that genetic background significantly impacts disease

progression and suggest that B6rTg4510 mice provide a useful model for investigating early pathogenic events preceding neurodegeneration, thereby facilitating mechanistic studies of Alzheimer's disease and related tauopathies.

Disclosures: Y. Nomura: None. **R. Yanai:** None. **T. Minamihisamatsu:** None. **C. Seki:** None. **H. Mizuma:** None. **R. Koike:** None. **S. Uchida:** None. **M. Higuchi:** None. **M. Shimojo:** None. **H. Misawa:** None. **N. Sahara:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

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Program #/Poster #: PSTR352.07/V25

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

Support: NCATS KL2TR002385
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R56 NS111052
R01AG077576
UL1TR002384

Title: Lateral ventricle enlargement partially mediates the relationship between white matter hyperintensity burden and interstitial fluid dynamics indexed by DTI-ALPS in Alzheimer's disease

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Abstract: RATIONALE Despite the broad application of diffusion tensor imaging along the perivascular space (DTI-ALPS) as a surrogate marker of glymphatic function, this interpretation is increasingly contested. DTI-ALPS is derived from the diffusivity ratio between directions along and perpendicular to deep medullary veins (DMV) in white matter adjacent to lateral ventricles (LV). The contributions of structural and vascular features, including influences from white matter injury and brain atrophy, and whether these differ by amyloid-beta (Aβ) status, remain undefined. Here, we evaluate the associations between structural features, vascular risk, LV volume, and DTI-ALPS in a cohort stratified by Aβ PET status. **METHODS** Multimodal MRI included DTI, T2-FLAIR, T2- and T1-weighted sequences. PiB PET provided Aβ stratification. Covariates included WMH volume, enlarged perivascular space (PVS) volume, LV volume, and DMV count. ROI segmentation was performed with FreeSurfer and volumetrics were normalized by intracranial volume. Multivariable linear regression, controlling for age and sex, identified predictors of DTI-ALPS across the whole group and stratified by Aβ status.

Significant predictors were then entered into mediation analysis with bootstrapped confidence intervals.
RESULTS No difference in age (70±8.6 years) or sex (59% female) was observed across groups (64 Aβ+/128 Aβ-). Aβ+ individuals had a higher LV volume (p=0.0005) and a lower DMV count (p=0.031), with no difference in WMH, PVS, or DTI-ALPS index. Multivariable regression found LV volume (β=−0.063, p<0.001) and WMH burden (β=−0.009, p=0.028) were independent predictors of lower DTI-ALPS (adjusted R^2=0.36), with no contribution from PVS burden or DMV count. When stratified by Aβ status, LV volume independently predicted lower DTI-ALPS in both Aβ+ (β=−0.062, p<0.001) and Aβ- participants (β=−0.073, p<0.001), while WMH burden was an independent predictor in only Aβ+ individuals (β=−0.015, p=0.003; adjusted R^2=0.43). Mediation analysis showed LV enlargement partially mediates the association between WMH burden and DTI-ALPS (proportion mediated: 36.3%, $CI_{95\%}$ 4.9-71.8%, p=0.034).**CONCLUSION** DTI-ALPS variance is driven by LV enlargement regardless of Aβ status, with WMH burden emerging as an additional independent predictor in Aβ+ participants. LV enlargement partially mediates the effect of WMH burden on DTI-ALPS, suggesting that periventricular structural changes are a key driver in the association of white matter injury to DTI-ALPS. PVS burden and DMV count were not contributing features, together challenging the interpretation of DTI-ALPS as a surrogate of glymphatic function.

Disclosures: S.A. Keil: A. Employment/Salary (full or part-time):; Weill Cornell Medicine, Department of Radiology. **T.A. Butler:** A. Employment/Salary (full or part-time):; Weill Cornell Medicine, Department of Radiology. **Y. Li:** A. Employment/Salary (full or part-time):; Weill Cornell Medicine, Department of Radiology. **L. Zhou:** A. Employment/Salary (full or part-time):; Weill Cornell Medicine, Department of Radiology.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.08/V26

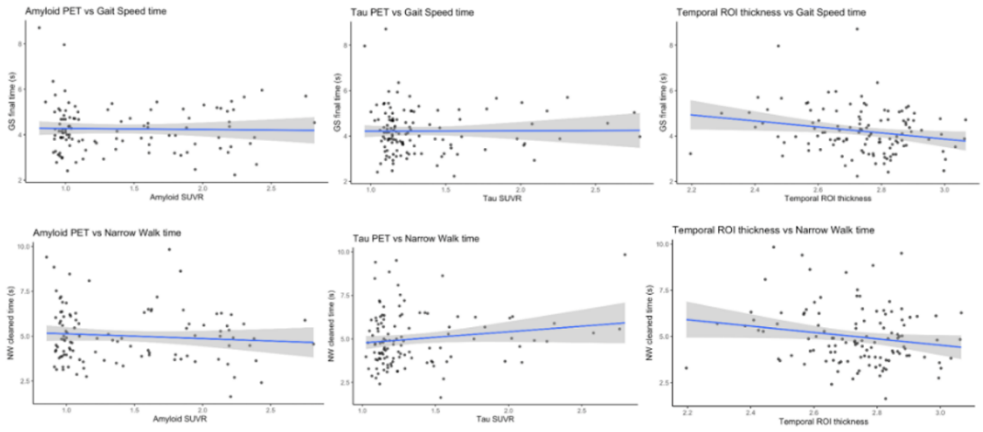
Topic: C.02. Alzheimer's Disease and Other Dementias

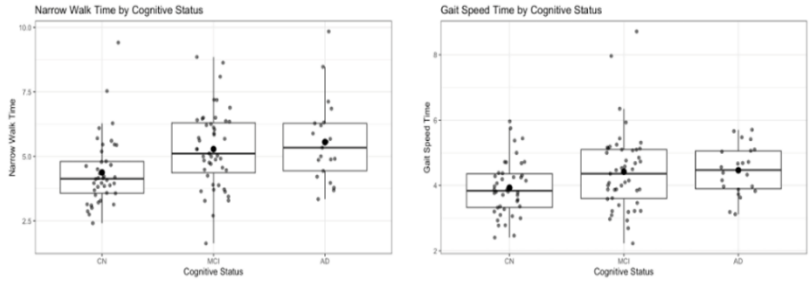
Support: NIA P30 AG072947

Title: Associations between Gait Performance and Alzheimer’s Disease Imaging Biomarkers in Older Adults

Authors: *Z. SUI[1], M. M. RUNDLE[4], K. ALPHIN[4], M. RUDOLPH[5], S. CRAFT[2], S. L. RISACHER[3];
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Abstract: Gait impairment is increasingly recognized as an early and clinically meaningful marker of neurodegeneration in Alzheimer's disease (AD). While prior work has linked gait decline to AD-related pathology, the relative contributions of amyloid deposition, tau pathology, and neurodegeneration remain unclear. We examined associations between gait performance and AD-related imaging biomarkers in older adults from the Wake Forest Alzheimer's Disease Research Center (ADRC; n = 123). Gait performance was assessed using Gait Speed (GS) and Narrow Walk (NW) test from the Expanded Short Physical Performance Battery (ESPPB). Imaging measures included amyloid PET burden ([^{11}C]PiB global cortical SUVR), tau PET burden ([^{18}F]flortaucipir meta-temporal SUVR), and temporal lobe cortical thickness (TempROI). Linear regression models adjusted for age, sex, and years of education were used to evaluate associations between imaging biomarkers and gait outcomes. Reduced temporal lobe cortical thickness was associated with poorer GS (β = -1.47, p = 0.0099) and NW performance (β = -1.80, p = 0.0469). Tau burden was not associated with GS but demonstrated a trend-level association with NW (β = 0.76, p = 0.056). Amyloid burden was not significantly associated with either gait measure. In secondary analyses, individuals diagnosed with mild cognitive impairment (MCI) and AD exhibited poorer gait performance than cognitively normal (CN) participants, with stronger effects observed for NW than GS. These findings suggest that gait impairment is more strongly associated with cortical neurodegeneration than with either amyloid or tau pathology. More complex gait tasks may be particularly sensitive to functional changes associated with AD-related neurodegeneration and disease progression.





Disclosures: Z. Sui: None. **M.M. Rundle:** None. **K. Alphin:** None. **M. Rudolph:** None. **S. Craft:** None. **S.L. Risacher:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.09/V27

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

Support: USAMRAA Grant HT94252310224

Title: Associations Between T1/T2 MRI Ratios and Cognitive Performance in Aging Veterans

Authors: *K. RAO[1], M. REIN[1], Y. XIONG[1], S. D. NEWMAN[2];
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Abstract: Aging is associated with microstructural brain changes that contribute to variability in cognitive performance. The T1-weighted/T2-weighted (T1/T2) MRI ratio is a myelin-sensitive marker of cortical and white matter integrity, and prior studies have demonstrated associations between T1/T2 alterations and cognitive decline in Alzheimer's disease. In the current study, we focused on veterans aged 55 years and older, a population that may be particularly vulnerable to neurocognitive aging due to increased exposure to neurotrauma, including head injuries, blast exposures, burn pit exposure, and psychosocial trauma. Structural MRI data were used to generate T1/T2 ratio maps, and regression analyses examined associations between regional T1/T2 ratios and performance on the Montreal Cognitive Assessment (MoCA), a screening measure commonly used to detect mild cognitive impairment and early dementia. Consistent with prior research, MoCA scores tended to decline with age, although this association was not statistically significant, likely due to the study's recruitment strategy and restricted range of cognitive functioning. Correlation analyses revealed no significant association between hippocampal T1/T2 ratios and MoCA scores. In contrast, T1/T2 ratios within the entorhinal cortex showed a positive association with cognitive performance. To further examine these relationships, regression analyses tested the interaction between age and MoCA scores in predicting regional T1/T2 ratios. A significant age × MoCA interaction was observed for the entorhinal cortex, whereas no significant effects were detected for the hippocampus. These findings suggest that microstructural alterations captured by T1/T2 ratios may be more readily detectable in the entorhinal cortex than in the hippocampus during the early stages of cognitive decline. The results further support the possibility that entorhinal cortex T1/T2 measures may serve as a sensitive marker of age-related microstructural changes associated with emerging cognitive impairment.

Disclosures: K. Rao: None. **M. Rein:** None. **Y. Xiong:** None. **S.D. Newman:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.10/V28

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

Support: USAMRAA Grant HT94252310224

Title: Associations Between White Matter Integrity and Psychological Wellbeing in Aging Veterans

Authors: *H. JACKSON[1], Y. XIONG[2], M. REIN[2], S. D. NEWMAN[3];
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Abstract: Environmental stressors have been shown to negatively affect cognitive functioning and psychological well-being in aging adults, particularly among veterans. Exposure to chronic environmental stressors may increase vulnerability to adverse mental health outcomes, including post-traumatic stress disorder (PTSD), depression, suicidality, and dementia. Despite these associations, relatively little research has examined how environmental stressors influence white matter integrity and other neural substrates that may underlie psychological health in older veterans. We hypothesize that veterans exhibiting poorer cognitive functioning and psychological well-being will demonstrate lower fractional anisotropy (FA) and higher radial diffusivity (RD), indicative of reduced white matter integrity. In the current study, diffusion tensor imaging (DTI) data were collected from veterans aged 55 years and older using magnetic resonance imaging (MRI). FA and RD values were extracted using FSL to assess white matter integrity. Regression analyses examined associations between these neuroimaging markers and measures of psychological well-being, including psychiatric symptom burden and suicidality. Preliminary findings indicate that FA within the superior longitudinal fasciculus (SLF) is associated with suicidal behavior. These findings suggest that alterations in white matter integrity may be linked to specific aspects of psychological risk in older veterans and highlight the need for further investigation of neural mechanisms underlying mental health and well-being in this population.

Disclosures: H. Jackson: None. **Y. Xiong:** None. **M. Rein:** None. **S.D. Newman:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.11/W1

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

Title: 1D, 2D, 3D: Cross-scale cell typing and spatial analysis of the APP/PS1 Alzheimer's disease mouse brain using single-nucleus RNA sequencing, cyclic multiplexed immunofluorescence, and light-sheet microscopy

Authors: *K. W. RYCHEL-PENN, C. SPLAINE, C. EMERY, K. KERN, B. YEAGY; Miltenyi Biotec, San Diego, CA

Abstract: Modern tissue profiling spans complementary scales. Single-nucleus RNA sequencing (snRNA-seq) resolves transcriptome-wide cell identity but discards spatial context and reports transcript rather than protein state; cyclic multiplexed immunofluorescence captures dozens of proteins with 2D spatial context in a single section; and light-sheet fluorescence microscopy (LSFM) reconstructs a limited marker set across an intact 3D volume. No single modality reveals both molecular breadth and spatial organization, which together are central to understanding neurodegeneration. We integrate all three across the APP/PS1 (ARTE10) amyloidosis model of neurodegeneration and C57BL/6NTac wild-type (WT) controls (one brain per genotype per modality; female, 24-30 weeks). snRNA-seq (10x Genomics, Flex Gene Expression) defines high-confidence transcriptomic cell types and informs panel design. A 40-marker cyclic immunofluorescence panel applied to full coronal sections recovers these cell types with 2D spatial context, and the section planes are mapped onto the 3D volumes. Cleared whole brains imaged by LSFM are registered to the Allen Mouse Brain Common Coordinate Framework (CCFv3). Within each modality we compare supervised gating against unsupervised clustering for cell typing and quantify their concordance; we then assess agreement of cell-type abundances across modalities, attributing discrepancies to sampled regions and available markers. Focusing on microglial and infiltrating immune states, we test how proximity to amyloid plaques, dystrophic glia, vasculature, and white- versus gray-matter compartments relates to cell state and marker expression. Spatial enrichment is evaluated at single-cell resolution, comparing marker expression between cell types and between neighbors and non-neighbors of a given population (t-tests for continuous expression; Fisher's exact tests for categorical labels). We demonstrate that transcriptomic, 2D proteomic, and 3D anatomical views converge on a coherent description of cellular states and their spatial organization in the degenerating brain, establishing a transferable framework for cross-scale, spatially resolved study of neurodegeneration.

Disclosures: K.W. Rychel-Penn: A. Employment/Salary (full or part-time):; Miltenyi Biotec. **C. Splaine:** A. Employment/Salary (full or part-time):; Miltenyi Biotec. **C. emery:** A. Employment/Salary (full or part-time):; Miltenyi Biotec. **K. Kern:** A. Employment/Salary (full or part-time):; Miltenyi Biotec. **B. Yeagy:** A. Employment/Salary (full or part-time):; Miltenyi Biotec.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.12/W2

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

Support: NIH - AG088683
NIH - G083940
NIH - U54AG054345-08
T32AG071444

Title: TOX-AD: Neurometabolic Network Reorganization Metal/Metalloid-Exposed Dependents in AD Mouse Models.

Authors: *L. CEOTTO FREITAS LIMA[1], K. P. KOTREDES[5], J. A. MONCASTER[7], S. PERSOHN[2], K. ELDRIDGE[3], J. K. CHONG CHIE[4], O. MINAEVA[8], G. R. HOWELL[6], L. E. GOLDSTEIN[9], P. R. TERRITO[10];
[1]Indiana Univ., Indianapolis, IN; [2]Stark Neurosci., Indiana Univ., Fishers, IN; [3]Stark Neurosci., [4]Stark Neurosci. Res. Inst., Indiana Univ., Indianapolis, IN; [5]Res., [6]The Jackson Lab., Bar Harbor, ME; [8]Med., [7]Boston Univ., Boston, MA; [9]Mol. Aging and Develop. Lab., Sch. of Med., Boston, MA; [10]Med., Indiana Univ. Sch. of Med., Indinanapolis, IN

Abstract: Background: Metal/metalloid neurotoxicants are suspected modifiers of Alzheimer's Disease (AD) pathobiology. However, the molecular mechanisms underlying gene-by-environment (GxE) interactions during aging remain unclear, underscoring the importance of investigating the exposome in AD pathobiology. Thus, we hypothesize that exposures to arsenic (As), cadmium (Cd), and lead (Pb) alter neural connections and their roles in cognition and disease, thereby potentiating AD pathogenesis in a toxicant-specific, neurodevelopment-sensitive, and age-dependent manner. **Methods**: MODEL-AD humanized mouse models (B6J.hAPOE3.hAβ.hMAPT, B6J.hAPOE4.hAβ.hMAPT) were exposed to As, Cd, or Pb via drinking water at human-relevant concentrations (e.g., 20, 50, and 200 ppm, respectively). After exposure, we performed neuroimaging (PET/CT) to assess amyloid-β (Aβ) deposition (18F-AV45), neurometabolism (18F-FDG), and functional connectivity. Mice were euthanized, perfused, and tissues were harvested for further analysis. Using covariance analysis and consensus clustering, we evaluated changes in functional connectivity across AD stages by calculating whole-brain entropy, degree distribution, nodal connection strength, and clustering coefficients from 18F-FDG images. Finally, we separately analyzed 18F-FDG and 18F-AV45 for positive and negative regional correlations. **Results:** The neurotoxicants accumulated in the brain, leading to aberrant Aβ deposition in 4-month-old B6J.hAPOE3.hAβ.hMAPT mice and in 10-month-old female B6J.hAPOE4.hAβ.hMAPT mice. Additionally, metabolic connectivity analysis revealed changes in degree distribution, connection strength, and clustering coefficients due to metal/metalloid exposure, suggesting metabolic brain network reorganization, either as compensatory mechanisms or as signs of pathological disruption. Both Aβ deposition and metabolic connectivity analysis were sex- and metal-dependent and modulated by the estrous cycle in Control/As/Cd/Pb, respectively, suggesting that estrogen-metal interactions also significantly impact Aβ deposition and reorganization of the metabolic brain network. **Conclusion:** Mice exposed to metals/metalloids showed region-specific metabolic alterations in the brain and Aβ plaque deposition. This revealed toxicant-specific neurometabolic alterations, enabling us to correlate them with similar disease signatures observed in patients by assessing metabolic alterations in brain connectivity. Thus, investigating GxE interactions highlights the importance of integrating the exposome into the AD field and of analyzing its progression with age.

Disclosures: L. Ceotto Freitas Lima: None. **K.P. Kotredes:** None. **J.A. Moncaster:** None. **S. Persohn:** None. **K. Eldridge:** None. **J.K. Chong Chie:** None. **O. Minaeva:** None. **G.R. Howell:** None. **L.E. Goldstein:** None. **P.R. Territo:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.13/W3

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

Support: NIH/NIA RF1AG085638

Title: Brain states with strong activity in the cortical association system last longer in participants who do not have Alzheimer's disease

Authors: *D. S. JIN[1], A. T. KAHN[1], P. STEWART[2], G. LING[1], Y.-H. FANG[1], K. M. VISSCHER[3];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Univ. of Alabama, Birmingham, Homewood, AL; [3]Neurobio., Univ. of Alabama, Birmigham, Birmingham, AL

Abstract: Dynamic patterns of neural activity characterize the capability of the brain to maintain a given brain state. Several studies have used static connectivity measures to show that patients with Alzheimer's disease (AD) have aberrant patterns of functional connections. These static measures may not tell the whole story underlying patients' deficits, however, as they cannot characterize the dynamics of brain states. Such dynamics can be measured using co-activation patterns (CAPs), a method which identifies recurring single-timepoint whole-brain patterns of BOLD signals. We hypothesize that AD is associated with a decreased duration of brain states involving coordinated activity within networks important for complex cognitive tasks. Standard CAP methods cannot directly test this as they do not identify persistence of a given cortical network. We used a novel method for identifying persistence of brain states involving a given brain network to examine how network persistence is impacted by AD.
To study dynamics of individual networks, we needed to identify whether the brain's state at a given time involved activity in a given network. Typical CAP methods define a set number of states, and examine their persistence. However, two different CAPs often involve strong activity of the same cortical network. Thus, "true" network persistence is not measured by CAP persistence. We developed a method to identify the persistence of brain states involving a given network. We first parcellated participant brains into 333 parcels, each of which is assigned to one of 10 networks, using the Gordon atlas (2016). Then, we identified eight CAPs in our sample. In each CAP, we determined whether a given network was involved in that CAP by calculating the average centroid values of parcels in that network, and observing whether that value exceeded a magnitude cutoff. We calculated "network persistence" as the number of continuous timepoints assigned to any CAP involving a given network. Average persistence for each network was calculated for each of 329 participants from the Alzheimer's Disease Neuroimaging Initiative

(ADNI) dataset.
We investigated whether the network persistence of our CAPs differed with disease severity in participants with AD, mild cognitive impairment, and healthy controls. We observed decreasing network persistence with increasing disease severity in the default mode, dorsal attention, and visual networks.
These findings demonstrate that our method can identify network-specific differences in neural dynamics. Further, they support our hypothesis that neural dynamics are impacted as AD progresses, shortening the duration of some brain states.

Disclosures: D.S. Jin: None. **A.T. Kahn:** None. **P. Stewart:** None. **G. Ling:** None. **Y. Fang:** None. **K.M. Visscher:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.14/W4

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

Title: Instantaneous spatial connectivity is a generalizable EEG Biomarker for single-trial detection of Alzheimer’s Disease and Frontotemporal Dementia.

Authors: *G. OSEI, L. N. REBOLLAR-HERNANDEZ, N. SOLAGRATIA, D. W. GATLIN, D. DASH;
Tarleton State Univ., Stephenville, TX

Abstract: Dementia, including Alzheimer’s disease (AD) and Frontotemporal dementia (FTD), presents overlapping clinical symptoms that challenge early diagnosis. Electroencephalography (EEG) offers a non-invasive, cost-effective alternative for capturing real-time neurophysiological signatures. However, existing classification frameworks often fail to account for within-session data leakage or ensure true generalizability across unseen subjects, frequently leading to inflated accuracy metrics. This study addresses these gaps through a two-stage analytical pipeline: Using a 19-channel resting-state EEG data sets of 88 participants (36 AD, 23 FTD, and 29 controls), first, we evaluated a comprehensive suite of baseline time-domain features including Mean, Kurtosis, Covariance, RMS, in comparison to the hypothesized instantaneous spatial connectivity feature (Log-Eigen-Covariance), to identify the most discriminative representation. Next, we optimized this marker across different neural oscillations. We assessed generalizability using two validation frameworks: (1) evaluating within-subject sequential temporal split (training on the first four minutes and testing the last one minute) and (2) achieving subject-independent generalization via strict leave-one-subject-per-class cross-validation. For temporal generalization, Log-Eigen-Covariance features achieved the best 3-class single trial classification accuracy (0.96 ± 0.18) with an LGBM classifier, outperforming all time-domain features (Holm-corrected Wilcoxon signed-rank: vs. Mean, Kurtosis, RMS all $p < 0.001$, $r \geq 0.54$; vs. Covariance $p = 0.014$, $r = 0.33$) and all other classifiers (all $p \leq 0.001$, $r \geq 0.94$). Under subject-

independent evaluation, these features paired with RidgeClassifierCV attained a peak mean accuracy of 57.1% significantly outperforming all time-domain features (Holm-corrected Wilcoxon signed-rank: vs. Mean, Variance, RMS all $p < 0.001$, $r \geq 0.54$; vs. Covariance $p = 0.014$, $r = 0.33$). Deep learning models achieved modest subject-independent accuracies: EEGNet (0.607 ± 0.337), Transformer (0.576 ± 0.340), CNN-LSTM (0.564 ± 0.344), and GNN (0.563 ± 0.308), all significantly lower than within-subject temporal split performance (Holm-corrected Wilcoxon signed-rank tests, all $p < 0.001$, $r = 0.70$-0.86). These results indicate that reliable single-trial classification depends on subject-specific calibration. Instantaneous EEG spatial connectivity may serve as a biomarker for distinguishing overlapping signals of AD and FTD, supporting a scalable approach for EEG-based diagnosis.

Disclosures: G. Osei: None. **L.N. Rebollar-Hernandez:** None. **N. Solagratia:** None. **D.W. Gatlin:** None. **D. Dash:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.15/W5

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

Support: Coins for Alzheimer's Research Trust (CART)

Title: Systematic Optimization of Multiplexed Immunolabeling in Cleared Human Brain Tissue with Alzheimer’s Disease

Authors: *H. ZHU[1], L. ESTRELLA[2], V. CHANCHYKOV[3], R. E. BENNETT[4], B. HYMAN[3], T. J. ZWANG[4];
[1]Neurol., Mass Gen. Brigham, BOSTON, MA; [2]Mass Gen. Hospital/Harvard Med. Sch., Boston, MA; [3]Neurol., Massachusetts Gen. Hosp., Boston, MA; [4]Neurol., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Tissue-clearing methods such as CLARITY and SHIELD enable large-volume imaging of immunolabeled tissue, offering substantial benefits for the neuropathological assessment of Alzheimer’s disease and related dementias (ADRD). However, their application in postmortem human brain tissue remains limited by inconsistent antibody penetration, variable staining quality, and high troubleshooting costs. To overcome these barriers, we systematically optimized protocols for formalin-fixed human brain tissue (Massachusetts Alzheimer’s Disease Research Center Brain Bank), validating conditions for over two dozen ADRD-relevant targets. We generated tissue libraries of ~1 mm^3 human brain samples to evaluate 14 modified protocols using 49 total antibodies and dyes across three donors. By adjusting a single parameter from the baseline (such as delipidation duration, antigen retrieval temperature, or buffer composition), we successfully isolated the effects of individual variables on tissue staining outcomes. Our panel targeted key cellular and ADRD-related structures, including neurons, microglia, astrocytes,

vasculature, synapses, mitochondria, tau pathology, and amyloid-β. All together, we screened a total of 49 antibodies and dyes, out of which 41 had demonstrated reproducible staining, and 8 did not work in any of the conditions tested. There was not one universal condition that worked for every antibody, but some conditions worked consistently for a large number of antibodies. We then evaluated these stains using multi-round multiplexed fluorescent imaging to maximize co-registered targets within the same tissue. We compared several cyclic staining strategies, including peroxide- and photobleaching-based CycIF, SDS and β-mercaptoethanol antibody stripping, and oligonucleotide-conjugated antibodies (SignalStar). SignalStar proved most effective for both staining and fluorescence removal by successfully resolving 8 targets across 4 imaging rounds in the same 1-mm-thick tissue. Together, these optimized protocols provide a scalable and effective framework for high-dimensional spatial profiling of neuroscience.

Disclosures: H. Zhu: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Cell Signaling Technology. **L. Estrella:** None. **V. Chanchykov:** None. **R.E. Bennett:** None. **B. Hyman:** None. **T.J. Zwang:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.16/W6

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

Title: Synaptic Aβ Nanoclusters Drive Nanoscale Remodeling of Excitatory Inputs onto Parvalbumin Interneurons in Alzheimer’s Disease

Authors: *S. LEE, J. KANG;
The Herbert Wertheim UF Scripps Inst. for Biomed. Innovation & Technol., Jupiter, FL

Abstract: Parvalbumin-positive interneurons (PV-INs) are fast-spiking GABAergic neurons essential for maintaining excitation-inhibition balance and coordinating pyramidal neuron activity through gamma oscillations. Because a single PV-IN can influence large ensembles of excitatory neurons, even subtle PV-IN dysfunction may disproportionately disrupt circuit stability and cognition. Emerging evidence suggests that PV-INs are altered very early in Alzheimer’s disease (AD). In amyloid mouse models, PV-IN hyperexcitability and dysfunction emerge during early Aβ accumulation, preceding overt changes in pyramidal neuron excitability. However, the molecular basis of PV-IN vulnerability remains poorly understood. Recent expansion microscopy (ExM) studies have revealed Aβ nanoclusters that are not readily resolved by conventional microscopy, as well as their spatial association with synaptic proteins. Building on these findings, I investigate whether excitatory synapses onto PV-INs undergo pathology-dependent nanoscale remodeling and whether these alterations are linked to synaptic Aβ nanoclusters. To test this hypothesis, my approach combines cell-type-specific proteomic screening with ExM in an AD mouse model. After profiling of disease-stage-dependent proteomic changes at PV-IN-specific excitatory synapses, ExM is utilized to determine the

spatial relationship between synaptic Aβ nanoclusters and altered synaptic structures at nanoscale resolution. By defining synaptic nanostructures selectively associated with PV-IN vulnerability, this work aims to elucidate the origins of early inhibitory circuit abnormalities in AD and identify novel molecular targets that may be obscured in bulk tissue analyses.

Disclosures: S. Lee: None. **J. Kang:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.17/W7

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

Title: EEG Stratification of Alzheimer's and Frontotemporal Dementia via Photic-Stimulation

Authors: *L. N. REBOLLAR-HERNANDEZ, G. OSEI, D. DASH;
Tarleton State Univ., Stephenville, TX

Abstract: Overlapping clinical symptoms between Alzheimer's disease (AD; 60-80% of cases) and frontotemporal dementia (FTD; 10-15%) complicate accurate differential diagnosis. While electroencephalography (EEG) provides a non-invasive, cost-effective tool to monitor neurodynamic in AD, its application in FTD remains under-researched, leaving reliable stratification between these two disorders limited. We investigated EEG-derived neurophysiological differences among individuals with AD, FTD, and healthy controls (HC) during photic stimulation. Using a 19-electrode resting-state EEG dataset collected from 88 subjects (AD: 36, FTD: 23, HC: 29) during different photic stimulation frequencies (5, 10, 15, and 20 Hz), we examined spectral power, coherence, and desynchronization across regional brain activity and neural oscillations to identify group-level EEG differences across these conditions. During photo stimulation both FTD and AD exhibited divergent EEG profiles compared to HC; Statistical comparisons were made using Linear Mixed Effects models and multi-way ANOVAs. To control for multiple comparisons, p-values were adjusted using Benjamin-Hochberg, FDR. Significant main effects were subsequently explored using Bonferroni-corrected post-hoc tests. Significance was set at an adjusted $p < 0.001$. AD demonstrated widespread slowing (increased theta across all frequencies and elevated 15 Hz delta), whereas FTD displayed restricted alterations (increased 15 Hz Beta and reduced 20 Hz alpha). AD showed a slow-wave hyper-synchronization pattern (increased delta/theta, reduced alpha coherence), contrasting with the fast-wave hyper-connectivity observed in FTD (increased beta/gamma, reduced alpha coherence). ERD analysis showed enhanced central beta-band desynchronization at 10 Hz in FTD and enhanced occipital beta-band desynchronization at 15 Hz in AD. These findings suggest that AD and FTD are associated with fundamentally different electrophysiological signatures. The widespread slow-wave activity in AD aligns with its characterization as a cortical slowing and disconnection syndrome, whereas the frontal fast-wave hyperexcitability observed in FTD may reflect disease-specific alterations in neural network

organization and cortical regulation. Ultimately, combining EEG with photic stimulation provides a sensitive, non-invasive approach for characterizing disease-specific patterns of brain dysfunction. These multi-measures demonstrate the immense potential of EEG-based biomarkers for advancing differential diagnosis and mapping the distinct neural mechanisms underlying AD and FTD.

Disclosures: L.N. Rebollar-Hernandez: None. **G. Osei:** None. **D. Dash:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.18/W8

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

Support: NIH Grant R01AG074552

Title: The PS19 mouse model for tauopathy shows abnormal brain microvascular remodeling and dysfunctional blood brain barrier

Authors: *A. F. CITALAN-MADRID[1], K. STANGIS[3], E. J. SU[4], D. A. LAWRENCE[5], G. G. MURPHY[2];
[2]MNI/MIP, [1]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [3]MNI, Univ. of Michigan, MNI, Ann Arbor, MI; [4]Intrnl. Med. - Cardiovasc. Div., Univ. of Michigan, Ann Arbor, MI; [5]Intrnl. Med., Univ. Michigan, Ann Arbor, MI

Abstract: Peripheral vascular etiologies remodel CNS vasculature, compromising the blood-brain barrier (BBB) and promoting dementia in Alzheimer's disease (AD). Although brain microvascular remodeling in AD was considered secondary to neuronal damage, its role remains understudied. Here, we investigated brain microvascular function using the tauopathy (PS19) mouse model, which expresses hyperphosphorylated tau protein. Using male and female PS19 mice and WT controls, we stained the brain microvasculature and used a tissue clearing method (CUBIC-L/R+) for confocal microscopy and vascular morphometric analysis in cortex and hippocampus. We also analyzed endothelial intercellular junctions, pericyte coverage, and neuroinflammation via microglia and astrocytes using immunofluorescence. Both male and female PS19 mice exhibited brain atrophy in hippocampal and cortical regions. Morphometric analysis showed that average vessel diameter was unaffected in CA1, dentate gyrus, retrosplenial, and piriform cortex; however, PS19 mice increased the vessel density and tortuosity, and reduced the vessel length compared to WT controls. Notably, the piriform cortex in PS19 males was the most affected area. Immunofluorescence revealed increased p-tau expression, corresponding to reduced pericyte coverage in the cortex and hippocampus. Furthermore, we observed a drastic morphological shift in microglial cells, which transitioned into a highly reactive ameboid shape. This morphological change was accompanied by a significant overexpression of the complement C3 (C3) protein, indicating an increased cellular

activation and phagocytic activity. Even more, a marked overexpression of CD68 and its specific colocalization with GFAP revealed high lysosomal activity in astrocytes, establishing a clear link to a robust, ongoing neuroinflammatory process within the brain tissue. Finally, PS19 microvessels showed reduced expression and loss of colocalization of the tight junction (TJ) proteins claudin-5 and zonula occludens-1 (ZO-1), indicating potential BBB destabilization. These data allow us to conclude that blood vessel remodeling and damage appear to be influenced, to some extent, by the sex and genotype of PS19 mice. Furthermore, the level of blood vessel damage seems to be different for each brain region. The observed damage in the brain microvasculature extended to pericyte cells, which can lead to microvascular instability alongside a dysfunction of claudin-5 and ZO-1. This, in turn, could trigger leakiness of the vascular endothelium and inflammation, as indicated by microglial and astrocytic activation.

Disclosures: A.F. Citalan-Madrid: None. **K. Stangis:** None. **E.J. Su:** None. **D.A. Lawrence:** None. **G.G. Murphy:** None.

Poster

PSTR352: Alzheimer's Disease: Imaging

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.19/W9

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

Support: NIH R21AG089718-01
NIH 5T32HL129964-10

Title: NOX2 inhibition to therapeutically target microgliosis, amyloidosis, and cerebrovascular dysfunction in Alzheimer’s disease

Authors: *A. N. JAMUS;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Alzheimer’s Disease (AD) is the leading form of dementia, characterized by cognitive decline and physiological hallmarks like amyloid plaque accumulation, tau pathology, and neuroinflammation. A primary driver of this pathology is oxidative stress caused by augmented reactive oxygen species (ROS), which, in turn, impairs vascular function and exacerbates inflammation. One major source of ROS is nicotinamide adenine dinucleotide phosphate (NADPH) Oxidase 2 (NOX2), a multicomponent, cell membrane-bound enzyme known to play a role in age-related neuronal and vascular damage. Thus, we hypothesize that the inhibition of NOX2 will ameliorate AD pathology and vascular dysfunction. To inhibit NOX2, small molecule CPP11G, developed in our laboratory, was used; it is predicted to compete for binding with NOX2 subunit p47^{phox}, binding to the enzyme’s core. This small molecule was injected into APP-PS1/CX3CR1-GFP mice, which overexpress amyloid precursor protein (APP) that is cleaved into Aß protein; and also express GFP on microglia for tracking. Mice were treated with CPP11G, and pathology was analyzed at monthly intervals until 18 mos. Physiological hallmarks

of AD were analyzed via cranial window and use of 2-photon (2P) microscopy. Aß plaque formation was visualized by Methoxy XO4 injection, and plaque volume was quantified via MATLAB. Microglia, a major phagocytic immune cell of the brain, typically clears Aß plaque formation. However, as AD progresses, microglia display an altered, less mobile morphology and phagocytic activity, releasing increased pro-inflammatory cytokines. This microgliosis is visualized by GFP-expressing microglia complemented by sulfur rhodamine injection for vascular visualization. Changes in morphology, mobility, and vascular association throughout the cortex are quantified via MATLAB. Vascular reactivity is also known to be compromised with AD progression, with decreased vasodilation over time altering proper vascular function. CO_2-induced vasodilation is detected by laser doppler flowmetry (LDF) probing and wide-field microscopy at the cranial window, quantified via MATLAB. Here, we show preliminary data highlighting halted Aß plaque formation, declined vascular reactivity, and microgliosis with and without CPP11G treatment. Further inquiry includes *ex vivo* analysis of NOX2 complexation and ROS production.

Disclosures: A.N. Jamus: None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.01/W10

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Natural Science Foundation of China Grant 82422025
National Natural Science Foundation of China Grant 824B200027

Title: AAV-Mediated miRNA-Scaffold RNAi Improves Survival and Behavior in uN2CpolyG Mice

Authors: *Y. ZHENG, J. DENG;
Peking Univ. First Hosp., Beijing, China

Abstract: Neuronal intranuclear inclusion disease (NIID) is a clinically heterogeneous neurodegenerative disorder caused by GGC repeat expansion in the 5' untranslated region of *NOTCH2NLC*, resulting in toxic polyglycine-containing proteins. No disease-modifying therapy exists for *NOTCH2NLC*-related NIID. We developed a stepwise CNS-directed RNAi strategy by screening six siRNAs targeting *NOTCH2NLC* transcripts in cellular models, incorporating the lead sequence into a miRNA scaffold, and delivering the construct with an AAV vector. Efficacy was tested in transgenic uN2CpolyG mice, with survival and neurological function as primary endpoints.
The lead *NOTCH2NLC*-targeting siRNA was packaged into an AAV-miRNA-siRNA vector and administered by intracerebroventricular injection at 4 weeks of age. Mice underwent longitudinal

open-field, novel object recognition, and rotarod testing. Cortical RNA sequencing was performed at 12 weeks, and lifespan was monitored prospectively.
Treated mice showed improved performance across open-field, novel object recognition, and rotarod paradigms relative to AAV controls. Median survival was prolonged from 152.0 to 182.5 days (log-rank chi-square = 19.93, df = 1, $P < 0.0001$; hazard ratio = 0.2132, 95% CI: 0.06741-0.6744). Cortical transcriptomic analysis showed treated animals shifting toward wild-type controls in principal component space, with predominant suppression of disease-associated gene expression changes. Pathway analyses identified significant enrichment of ribosomal and oxidative phosphorylation pathways among treatment-responsive genes, suggesting broad attenuation of disease-associated transcriptional alterations.
This study establishes a stepwise RNAi-based therapeutic strategy for *NOTCH2NLC*-related NIID, integrating cellular siRNA screening, miRNA-scaffold engineering, AAV-mediated CNS delivery, and in vivo efficacy assessment. Intracerebroventricular AAV-miRNA-siRNA improved behavior and markedly prolonged survival in uN2CpolyG mice, supporting AAV-mediated RNAi as a platform strategy for *NOTCH2NLC*-related disease and potentially other polyglycine repeat expansion disorders.

Disclosures: Y. Zheng: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Innovec Biotherapeutics. **J. Deng:** None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.02/W11

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: Grants-in-Aid from the Research Committee of CNS Degenerative Diseases, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health, Labour and Welfare Sciences Research Grants, the Ministry of Health, Labour and Welfare, Jap
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Title: NOTCH2NLC CGG repeat expansions contribute to amyotrophic lateral sclerosis through population-specific predisposing genetic architecture

Authors: *S. OKUBO[1], H. NARUSE[2], H. ISHIURA[1,3], T. TODA[4];
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Abstract: Repeat expansions can show striking population-specific architectures. In amyotrophic lateral sclerosis (ALS), the C9orf72 repeat expansion is common in European populations but rare in East Asians. Conversely, *NOTCH2NLC* CGG repeat expansions, established as the cause of neuronal intranuclear inclusion disease and enriched in East Asian populations, have been implicated in ALS in this population. However, the extent of their contribution to ALS and the population-specific genetic architecture underlying this association remain poorly understood. To clarify the role of *NOTCH2NLC* repeat expansions in ALS and the population-genetic background underlying their East Asian enrichment, we analyzed a Japanese sporadic ALS case series using repeat-primed PCR, flanking PCR, and long-read whole-genome sequencing (LR-WGS). We identified pathogenic-range CGG repeat expansions (>59 repeat units) in 3 of 463 patients with sporadic ALS (0.65%), and an additional patient harboring intermediate-length expansions (44-59 repeat units). A meta-analysis incorporating published association studies further supported a reproducible association between ALS and *NOTCH2NLC* expansions in East Asian populations. We next resolved haplotypes flanking the repeat locus using LR-WGS data from eight *NOTCH2NLC* expansion carriers (four ALS patients, four NIID patients). In parallel, we analyzed publicly available LR-WGS data from 1,011 individuals across diverse populations to examine the distribution of *NOTCH2NLC* repeat-size classes and linked variants. Consistent with previous reports, expanded alleles did not share a single extended founder haplotype. Instead, large-normal alleles, defined as 35-43 repeat units, were observed exclusively in East Asian individuals. We further identified five single-nucleotide variants (SNVs) on chromosome 1 that were linked both to expanded alleles in affected individuals and to large-normal alleles in East Asians. In East Asian populations, the frequency of these SNVs increased with repeat size, a pattern not observed in Europeans. Together, these results support a model in which East Asian-specific haplotypic backgrounds may predispose normal alleles towards large-normal alleles, creating a population-level reservoir from which pathogenic expansions can arise. These findings support *NOTCH2NLC* CGG repeat expansion as a genetic contributor to ALS in East Asians. More broadly, they suggest that susceptibility to NOTCH2NLC repeat expansion is shaped by a population-specific predisposing genetic background rather than by a single founder allele.

Disclosures: S. Okubo: None. **H. Naruse:** None. **H. Ishiura:** None. **T. Toda:** None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.03/W12

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 NS137233
R33 NS124965
R35 NS127253
R21 NS128630

Title: Transcriptomic profiling of SCA4 patient-derived iPSC neurons identifies disrupted neuronal and stress response pathways

Authors: *M. M. GANDELMAN[1], K. P. FIGUEROA[2], J. SUNDRUD[3], S. PAUL[2], D. R. SCOLES[2], S. M. PULST[4];
[1]Dept. of Neurol., Univ. of Utah, Salt Lake city, UT; [2]Neurol., Univ. of Utah, Salt Lake City, UT; [3]Univ. of Utah, Salt Lake city, UT; [4]Neurol., Univ. of Utah, SALT LAKE CITY, UT

Abstract: Spinocerebellar ataxia type 4 (SCA4) is a rare neurodegenerative disorder characterized by progressive cerebellar ataxia, sensory neuropathy, and degeneration of the cerebellum and sensory ganglia. SCA4 is caused by a pathogenic GGC-repeat expansion in ZFHX3, which encodes an expanded polyglycine tract. ZFHX3 is a transcription factor with essential roles in development and cellular homeostasis, and loss-of-function variants have been linked to neurodevelopmental disorders and childhood epilepsy. Altered ZFHX3 function has also been implicated in atrial fibrillation, where it is associated with metabolic and calcium-handling defects, suggesting that both loss- and gain-of-function mechanisms may contribute to disease.
To identify disease-associated pathways downstream of expanded ZFHX3, we generated iPSC lines from three SCA4 patients and two unaffected controls, engineered them for inducible NGN2 expression, and differentiated them into neurons. After three weeks in culture, triplicate samples from each subject were collected for RNA sequencing.SCA4 neurons expressed neuronal and glutamatergic markers, supporting successful neuronal induction. Transcriptomic analysis identified 23 upregulated and 14 downregulated genes in SCA4 neurons (adj p-value <0.05). Gene set enrichment analysis revealed SCA4 neurons present negative enrichment of pathways involved in neuronal identity and function, including axon and dendrite growth, synaptic organization, neurotransmitter transport, vesicle exocytosis, ion channel activity, and glutamatergic synapse function (adj p-value <0.05 and NES < -1.5). SCA4 neurons showed positive enrichment of oxidative phosphorylation, electron transport chain activity, ATP synthesis, Protein synthesis, DNA repair, p53-associated programs, apoptosis, and cell-death signaling (adj p-value <0.05 and NES > 1.5).
Together, these findings indicate that SCA4 patient-derived neurons exhibit impaired neuronal and synaptic programs, altered mitochondrial and metabolic activity, DNA damage responses, and activation of cell-death pathways. This transcriptomic profile suggests that both loss- and gain-of-function mechanisms involving ZFHX3 may contribute to SCA4 pathogenesis.

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Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.04/W13

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Natural Science Foundation of China (Grant NO.82301603)
China Postdoctoral Science Foundation (Grant NO. 2023M730676)
China Postdoctoral Science Foundation (Grant NO.2023TQ0078)

Title: Intranuclear Polyglycine Aggregation Drives Epigenetic Repression and Neurodegeneration Across PolyG Diseases

Authors: *S. ZHONG, Y. LIAN, J. DING;
Dept. of Neurol., Fudan Univ. Zhongshan Hosp., Shanghai, China

Abstract: Background:Polyglycine (polyG) diseases are an emerging group of repeat expansion disorders caused by CGG/GGC repeat expansions, including FXTAS, NIID, OPDM, and SCA4. A pathological hallmark shared across these disorders is the presence of polyG-containing intranuclear inclusions. However, the pathogenic significance of nuclear localization and the mechanisms underlying nuclear vulnerability remain poorly understood.Methods:To investigate the impact of subcellular localization on polyG toxicity, we generated a series of polyG expression constructs carrying nuclear localization signals (NLS), nuclear export signals (NES), or no targeting sequence and examined their effects in cultured cells and AAV-PHP.eB-based mouse models. Behavioral, pathological, transcriptomic, and epigenomic analyses were performed. Optogenetic tools were developed to operate the aggregation of polyG proteins in cells. Nascent RNA synthesis was assessed using EU incorporation assays, chromatin accessibility by ATAC-seq, and histone acetylation by immunostaining and immunoblotting. Human tissues from patients with polyG diseases were analyzed for validation. Therapeutic intervention was evaluated using the HDAC1/3 inhibitor NKL22.Results:Nuclear-targeted polyG proteins produced substantially greater toxicity than cytoplasmic polyG despite lower expression levels. In vivo, mice expressing nuclear polyG developed more severe motor deficits, cognitive impairment, neuronal loss, and gliosis than mice expressing cytoplasmic polyG. Transcriptomic analysis demonstrated extensive dysregulation of neuronal pathways associated with nuclear polyG accumulation. Mechanistically, intranuclear polyG aggregation caused a marked reduction in nascent RNA synthesis and global chromatin accessibility. These changes were accompanied by decreased H3K27 acetylation and increased HDAC3 expression in both experimental models and human polyG disease tissues. Importantly, pharmacological inhibition of HDAC1/3 partially restored H3K27 acetylation and RNA synthesis and ameliorated behavioral and neuropathological abnormalities.Conclusions:Our findings identify intranuclear polyG aggregation as a major determinant of polyG toxicity and establish epigenetic repression as a central downstream mechanism linking nuclear inclusions to neurodegeneration. These results provide a mechanistic framework for understanding selective nuclear vulnerability in polyG diseases and nominate HDAC-dependent chromatin dysregulation as a promising therapeutic target across this expanding class of repeat expansion disorders.

Disclosures: S. Zhong: None. **Y. Lian:** None. **J. Ding:** None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.05/W14

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NSFC Grant 82422025
Brain Science and Brain-like Intelligence Technology–National Science and Technology Major Project 2025ZD0217600

Title: GGC repeat expansions within novel ORFs are translated into toxic polyglycine proteins in OPDM

Authors: *J. DENG;
Dept. of Neurol., Peking Univ. First Hosp., Beijing, China

Abstract: The human genome is largely non-coding, with nearly half composed of repetitive elements such as microsatellites-short tandem repeats of 1-6 nucleotides. Expansions in specific microsatellites underlie over 60 neurological disorders; notably, our group previously identified pathogenic GGC repeat expansions in *GIPC1*, *NOTCH2NLC*, and *RILPL1*. However, most such expansions occur in non-coding regions, and their pathogenic mechanisms remain poorly understood. We show that GGC repeat expansions linked to diseases like oculopharyngodistal myopathy (OPDM/OPML) and neuronal intranuclear inclusion disease (NIID) lie within previously unidentified small open reading frames (ORFs) in non-coding sequences. These ORFs encode novel polyglycine-containing proteins. Antibodies against these proteins specifically label p62-positive inclusions, a hallmark pathology. Expressing these proteins alone recapitulates key disease features-including p62-positive aggregates, locomotor deficits, and muscle abnormalities in cellular, fly, and mouse models. The proteins vary widely in interactors, stability, aggregation, and toxicity. Our results highlight how the ORF context shapes the pathological properties of the polyglycine domain. We also identify a compound that suppresses expression of these proteins, suggesting a potential common therapeutic strategy. In summary, GGC expansions produce toxic polyglycine proteins through non-canonical translation, driving neurodegeneration and myopathy. This reveals a unified mechanism for multiple neurological diseases and underscores the functional importance of overlooked small ORF's in non-coding regions, redefining how non-coding mutations can lead to disease via de novo protein synthesis.

Disclosures: J. Deng: None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.06/W15

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: Brain Science and Brain-like Intelligence Technology-National Science and Technology Major Project (2025ZD0217600)
National Natural Science Foundation of China (82422025, 82171846, 824B200027, 82401635 and 82430059)

Title: Rad23B promotes ubiquitination and nuclear proteasomal degradation of polyGlycine protein in cellular and mouse models

Authors: *Y. WAN, Y. ZHENG, J. DENG;
Peking Univ. First Hosp., Beijing, China

Abstract: Neuronal intranuclear inclusion disease (NIID) is a polyglycine disease that primarily affects the neuronal and neuromuscular systems. However, the pathogenic mechanisms underlying polyglycine intranuclear inclusions remain poorly understood. Here, we developed a novel transgenic mouse model that faithfully recapitulates the multisystemic impairments associated with polyG intranuclear inclusions. Our findings demonstrate that polyG expression induces neurodegeneration, behavioral deficits, and age-dependent accumulation of uN2CpolyG aggregates across multiple tissues. Spatial proteomics analysis revealed that Rad23B is sequestered within intranuclear inclusions, leading to impaired proteasomal function. Rad23B promotes the ubiquitination and nuclear translocation of uN2CpolyG proteins for proteasomal degradation. Notably, overexpression of Rad23B mitigates both the pathological changes and toxic effects associated with NIID in both cellular and transgenic mouse models. These findings deepen our understanding of the mechanisms underlying polyG-induced toxicity and identify Rad23B as a promising therapeutic target for NIID and other polyG-related disorders.

Disclosures: Y. Wan: None. **Y. Zheng:** None. **J. Deng:** None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.07/W16

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH K08NS133300
Larry L. Hillblom Foundation

Title: High-throughput CRISPRi Screening for Modifiers of Polyglycine Aggregation in Neuronal Intranuclear Inclusion Disease

Authors: *B. RAMANI[1,2], K. BROWN[1], K. EHSANI[2], S. PICKARD[2], M. KAMPMANN[3]; [2]Pathology, [3]Inst. for Neurodegenerative Dis., [1]Univ. of California San Francisco, San Francisco, CA

Abstract: Neuronal intranuclear inclusion disease (NIID) is a progressive inherited neurodegenerative disorder caused by a CGG repeat expansion in the 5′ untranslated region (UTR) of the NOTCH2NLC gene. NIID has been described predominantly in individuals of East Asian ancestry, although its prevalence in other populations remains unclear. The repeat expansion results in expression of a highly aggregation-prone polyglycine-containing protein (uN2C-polyG), and the disease is neuropathologically characterized by widespread p62-positive intranuclear inclusions. Identifying factors that prevent aggregate formation or promote aggregate clearance could inform therapeutic strategies for NIID and related repeat expansion disorders. To investigate mechanisms of aggregation, we developed a FRET-based cellular model of uN2C-polyG aggregation in human cells. This model demonstrates time-dependent formation of detergent-resistant, p62-positive nuclear inclusions. High-throughput genetic screening of chaperone modifiers revealed a striking resistance of uN2C-polyG aggregates to modulation by endogenous chaperones, in contrast to a polyglutamine aggregation model in which chaperones exerted robust effects. Nevertheless, overexpression of select chaperones suppressed polyG aggregation, suggesting a possible expression level-dependent effect. Genome-wide screens to identify additional modifiers of aggregate formation and clearance are ongoing, alongside complementary in vivo studies in mouse models. We anticipate reporting these findings at the conference. In addition, we describe the identification of pathogenic NOTCH2NLC repeat expansions in individuals of Hispanic ancestry, representing, to our knowledge, the first such report. These findings suggest that NIID may be more prevalent in the United States than currently recognized and underscore the need for broader genetic testing.

Disclosures: B. Ramani: None. **K. Brown:** None. **K. Ehsani:** None. **S. Pickard:** None. **M. Kampmann:** None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.08/W17

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Natural Science Foundation of China Grant 82301603
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2023M730676

Title: Astrocytic polyG aggregation impairs neurovascular reactivity and contributes to behavioral dysfunction in neuronal intranuclear inclusion disease

Authors: *Y. LIAN[1], J. DING[1], S. ZHONG[2];
[1]Zhongshan Hospital, Fudan Univ., Shanghai, China; [2]Fudan Univ. Zhongshan Hosp., Shanghai, China

Abstract: Background:
Neuronal intranuclear inclusion disease (NIID) is caused by NOTCH2NLC GGC repeat-associated polyglycine (polyG) aggregation. In adult-onset NIID, most inclusions occur in astrocytes, and astrocytic abnormalities are increasingly recognized, particularly in episodic encephalitic or stroke-like manifestations. Autopsy studies showed perivascular preservation, dense GFAP-positive astrocytic processes around vessels, and altered AQP4 distribution, suggesting disturbed astrocyte-vascular interactions. However, the role of astrocytes in NIID remains unclear. We tested whether astrocytic polyG induces neurovascular dysfunction in vivo.
Methods:
AAV vectors expressing polyG under neuron- or astrocyte-specific promoters were delivered to mice. Behavior and survival were evaluated after injection. Astrocyte activation, astrocyte-vascular interface, and vascular remodeling were assessed by GFAP and vascular immunostaining. Cerebrovascular reactivity was examined by intrinsic signal optical imaging during whisker stimulation and 10% CO_2 challenge. Cortical oxygenation and functional connectivity were analyzed longitudinally.
Results:
Astrocytic polyG induced cognitive impairment and motor dysfunction at 3 months. In contrast, neuronal polyG caused marked motor impairment, whereas cognitive deficits were less evident. The two groups showed distinct survival patterns. Immunofluorescence revealed robust GFAP-positive astrocyte activation in astrocytic polyG mice, with astrocyte-vascular interface disruption and altered vascular density. Functional imaging showed impaired cerebrovascular reactivity, with attenuated responses to whisker stimulation and 10% CO_2. Longitudinal imaging revealed early cortical hyperoxygenation followed by reduced oxygen signals and weakened cortical network connectivity.
Conclusions:
Astrocytic polyG expression is sufficient to induce behavioral impairment, astrocyte activation, neurovascular interface disruption, vascular remodeling, impaired cerebrovascular reactivity, and altered survival. These findings support astrocytic dysfunction as contributor to NIID pathogenesis. The distinct survival pattern of astrocytic polyG mice may be related to episodic neurological manifestations and astrocyte-mediated neurovascular dysregulation.

Disclosures: Y. Lian: None. **J. Ding:** None. **S. Zhong:** None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.09/W18

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Elevated lysosomal cholesterol mediates mTORC1 activation contributing to pathogenesis in a CLN1 disease model

Authors: *A. P. APPU[1], M. B. BAGH[2], N. PLAVELIL[3], T. SADHUKHAN[4], A. B. MUKHERJEE[5];
[1]NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Bethesda, MD; [3]NICHD, [2]NIH, Bethesda, MD; [4]Eunice Kennedy Shriver Natl. Inst. of Child Hlth. and Human Develop., Natl. Inst. of Hlth. Office of Intramural, Bethesda, MD; [5]NICHD (National Inst. of Child Hlth. and Human Development), Natl. Inst. of Hlth. (NIH), Bethesda, MD

Abstract: The CLN1-disease is a devastating neurodegenerative lysosomal storage disorder (LSD) caused by mutations in the *CLN1* gene encoding palmitoyl-protein thioesterase-1 (PPT1), which depalmitoylates S-palmitoylated proteins (constituents of ceroid lipofuscin). Despite this discovery, the mechanism underlying CLN1 disease has remained elusive. Lysosomal cholesterol is reported to activate mTORC1 kinase, which suppresses autophagy contributing to neurodegeneration in most LSDs. We found that in the brain of *Cln1*$^{-/-}$ mice, which mimic INCL, lysosomal cholesterol level is significantly higher compared with that in their WT littermates. Intriguingly, we discovered that in *Cln1*$^{-/-}$ mice, the level of Niemann Pick C1 (NPC1), a polytopic lysosomal membrane protein that maintains lysosomal cholesterol homeostasis, was significantly lower compared with that in their WT littermates. We also found that NPC1 requires dynamic S-palmitoylation for trafficking to the lysosomal membrane and the lack of Ppt1 in *Cln1*$^{-/-}$ mice misroutes NPC1-protein to the plasma membrane. Moreover, Ppt1-deficiency impairs dynamic S-palmitoylation (palmitoylation-depalmitoylation) of NPC1 preventing its handover from adapter protein-2 (AP-2) to AP-3 essential for its trafficking to the lysosome and it was misrouted to the plasma membrane. Along with this defect, the level of oxysterol binding protein (OSBP) and its anchoring proteins-VAPA and VAPB mediated increased cholesterol on lysosomal limiting membrane mediated mTORC1-activation, which suppressed autophagy. Importantly, inhibition of OSBP by its inhibitor, OSW1, significantly lowered mTORC1-activation, and rescued autophagy in both human CLN1 disease lymphoblasts and protected the neurons in *Cln1*$^{-/-}$ mouse brain. Our findings uncover a previously unrecognized role of *Cln1*/Ppt1 in lysosomal cholesterol homeostasis and reveal a potential targetable pathway for CLN1 disease.

Disclosures: A.P. Appu: None. **M.B. Bagh:** None. **N. Plavelil:** None. **T. Sadhukhan:** None. **A.B. Mukherjee:** None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.10/W19

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Targeting Neurotoxic Astrocytes: A Human iPSC Platform Linking Inflammation, Lipid Dysregulation, and Neurodegeneration

Authors: T. MODEBADZE, X.-F. LI, S. GIACHETTI, H. SCOTT, ***E. MALAVASI**; Concept Life Sci. Ltd, Edinburgh, United Kingdom

Abstract: Astrocytes, the most abundant glial cells in the human central nervous system, play key roles in neuroprotection, immune regulation, and homeostasis. Under neuroinflammatory conditions, however, they adopt a reactive, neurotoxic phenotype that contributes to chronic inflammation and neurodegeneration. Secreted long-chain saturated fatty acids (LC-SFAs) have been implicated as key mediators of astrocyte-induced neurotoxicity. Notably, astrocyte dysfunction arises at pre-symptomatic stages of neurodegenerative disease, supporting their relevance as an early therapeutic target. Here, we further validated a human iPSC-derived astrocyte model of neurotoxic reactivity and assessed its functional impact on human neurons, alongside associated lipidomic changes. Astrocytes were stimulated with the pro-inflammatory "TIC" cytokine cocktail (30 ng/mL TNFα, 3 ng/mL IL-1α, 400 ng/mL C1q) in the presence or absence of anti-inflammatory compounds. Astrocyte conditioned medium (ACM) and cell lysates were collected for untargeted lipidomics and cytokine analysis. ACM was applied to human iPSC-derived neurons to assess effects on morphology and viability. TIC stimulation induced robust secretion of pro-inflammatory cytokines and chemokines, which was attenuated in a concentration-dependent manner by anti-inflammatory compounds. ACM from TIC-treated astrocytes triggered rapid neurite retraction and increased neuronal apoptosis, whereas ACM from compound-treated astrocytes did not induce neurotoxicity. Lipidomic profiling revealed marked TIC-driven remodelling of the astrocyte secretome, including increased release of LC-SFAs, consistent with reported neurotoxic lipid signatures. Collectively, these data demonstrate that human iPSC-derived astrocytes recapitulate key features of the neurotoxic reactive phenotype, including functional neurotoxicity and disease-relevant lipid alterations. This platform provides a translationally relevant system for interrogating astrocyte-driven mechanisms and evaluating therapeutic strategies targeting neuroinflammation.

Disclosures: T. Modebadze: A. Employment/Salary (full or part-time):; Concept Life Sciences Ltd. **X. Li:** A. Employment/Salary (full or part-time):; Concept Life Sciences Ltd. **S. Giachetti:** A. Employment/Salary (full or part-time):; Concept Life Sciences Ltd. **H. Scott:** A. Employment/Salary (full or part-time):; Concept Life Sciences Ltd. **E. Malavasi:** A. Employment/Salary (full or part-time):; Concept Life Sciences Ltd.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.11/W20

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: 2383891-KIM
NIH Grant 683813
4088061

Title: ABCD2 depletion in miR-33 Knockout mouse causes cerebral xALD-like syndrome.

Authors: M. TATE[1,5], ***S. CHUNG**[6,2], M. AL AMIN[2], H. CHUNG[8], B. KIM[3], H. KARAHAN[7], D. GUTIERREZ[4], L. C. DABIN[7], J. KIM[2];
[1]Med. Neurosci., [2]Dept. of Med. and Mol. Genet., [3]Dept. of Med. & Mol. Genet., [4]Med. and Mol. genetics, Indiana Univ. Sch. of Med., Indianapolis, IN; [5]Mol. & Human Genet., Baylor Col. of Med., Houston, TX; [6]MMGE, [7]Med. and Mol. Genet., Indiana Univ., Indianapolis, IN; [8]Houston Methodist Res. Inst., Houston, TX

Abstract: MicroRNA-33 (miR-33) regulates lipid metabolism through control of cholesterol and fatty acid homeostasis, but its physiological role in brain lipid homeostasis remains less understood. Here, we show that miR-33 knockout (KO) mice have a profound disturbance of cerebral fatty acid balance that resembles the biochemical signature of human X-linked adrenoleukodystrophy (X-ALD). miR-33 KO mice displayed increased C26:C22 and C24:C22 ratios, including accumulation of very long chain fatty acids (VLCFA) and reduction of multiple long chain fatty acids (LCFA) species. Intriguingly, proteomic analysis revealed that the peroxisomal fatty acid transporter ABCD2 is markedly depleted in the brains of miR-33 KO mice. ABCD2 has a functional redundancy with ABCD1, which harbors mutations that cause X-ALD. miR-33 KO primary astrocytes expressed less *Abcd2* and failed to induce its expression under VLCFA exposure. To test whether ABCD2 depletion underlies the fatty acid dyshomeostasis, we restored ABCD2 expression in astrocytes. ABCD2 overexpression substantially mitigated the astrogliosis observed in miR-33 KO mice, indicating that impaired peroxisomal transport contributes to glial activation. ABCD2 overexpression also reversed the altered brain fatty acid profile of miR-33 KO mice, reducing VLCFAs accumulation and replenishing LCFAs. In primary astrocytes, ABCD2 expression restored the lipid handling capacity of miR-33 KO astrocytes under the exogenous fatty acid load. Together, enhancing ABCD2 may represent a therapeutic strategy to resolve VLCFA accumulation and neuroinflammation in leukodystrophies. Overall, our findings identify a previously unrecognized relationship between miR-33 and ABCD2 that regulates peroxisomal VLCFA catabolism, a process crucial for brain health.

Disclosures: M. Tate: None. **S. Chung:** None. **M. Al Amin:** None. **H. Chung:** None. **B. Kim:** None. **H. Karahan:** None. **D. Gutierrez:** None. **L.C. Dabin:** None. **J. Kim:** None.

Poster

PSTR353: Repeat Expansion Disorders, Protein Aggregation, and Proteostasis in Neurodegeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.12/W21

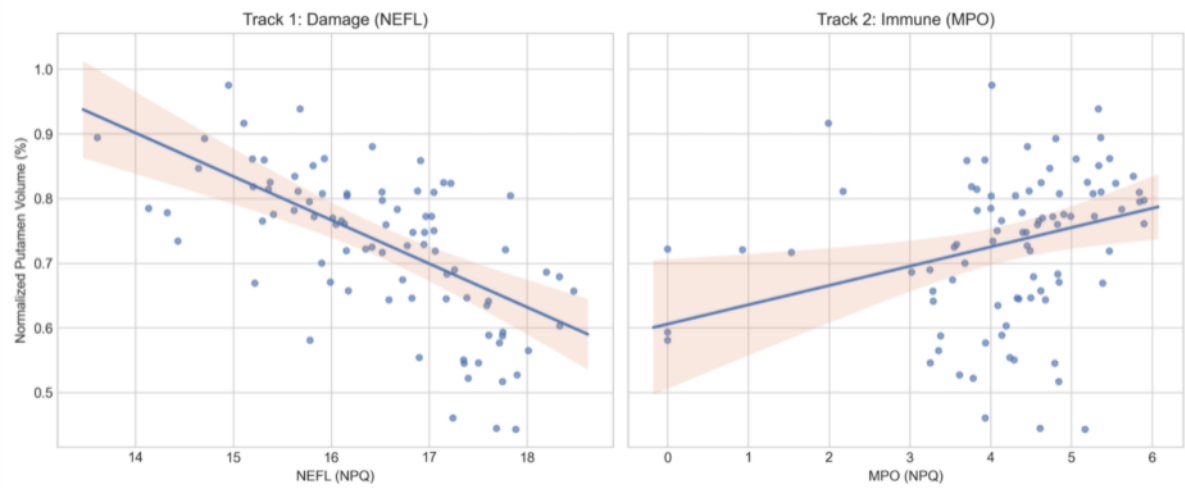
Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant U01NS103475
NIH Grant U01NS105509
NIH Grant R01NS040068
CHDI Grant A3917
CHDI Grant A6266

Title: Extending the Two-Track CSF Biomarker Framework in Huntington's Disease: Myeloperoxidase Defines a Complementary Immune-Oxidative Axis Independent of Neuroaxonal Injury

Authors: *J. D. CLEMSEN[1], H. J. BOCKHOLT[1], B. T. BAKER[1], V. D. CALHOUN[1], J. S. PAULSEN[2];
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Abstract: Background: Our prior work in Huntington's disease (HD) proposed a Two-Track cerebrospinal fluid (CSF) biomarker framework in Huntington's disease (HD) in which a neuroaxonal damage signal (Track 1; neurofilament light chain (NEFL)) and an immune-associated signal (Track 2; TNFRSF8/CD30) show opposing associations with striatal atrophy. Whether the model generalizes beyond immune-regulatory TNFR signaling to orthogonal immune/oxidative mechanisms remains unclear. Methods: We analyzed CSF proteomics (NPQ), MRI-derived normalized putamen volume, and disease burden in a cohort for CAG-age-product (CAP) score, sex, NEFL, and myeloperoxidase (MPO). Primary analyses included bivariate visualization of NEFL and MPO versus putamen and multivariable regression predicting putamen volume including CAP score and sex. Model comparison evaluated CAP versus age-adjusted specifications. Secondary analyses included sex-difference testing, correlation screening with FDR correction, and mediation analyses assessing directionality between CAP, putamen, and MPO. Results: Normalized putamen volume was strongly associated with CAP score in volumetric screening. NEFL was negatively associated with putamen volume, consistent with neuroaxonal injury. In contrast, MPO showed a positive association with putamen volume (Figure 1). In a CAP-adjusted multivariable model, NEFL remained independently negative and MPO independently positive, while CAP score retained an expected negative association. Conclusions: These results extend Track 2 to an orthogonal immune/oxidative marker (MPO). The opposing and independent associations of NEFL and MPO with putamen volume support a broadened Two-Track model in which immunological biology comprises multiple separable mechanisms beyond immune regulation alone.



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Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR354.01/W22

Topic: B.09. Glial Mechanisms

Support: John and Maurine Cox Endowed Chair to FS

Title: intracerebroventricular IL-17A Administration Induces Microglia Activation but Produces Limited Cognitive Impairment in Adult Rats

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[1]Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeutics, Bryan, TX, Unit, Bryan, TX; [2]Neurosci. and Exptl. Therapeut., Texas A & M Univ., Bryan, TX; [3]Neurosci. and Exptl. Therapeut., Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeut., Bryan, TX

Abstract: Ischemic stroke triggers a sustained neuroinflammatory response resulting in secondary neurodegeneration and cognitive decline. Interleukin-17A (IL-17A), a pro-inflammatory cytokine elevated following stroke, has been associated with microglial activation and white matter injury. Our studies show that iv injection of microRNA mir20a-3p, given 4h after stroke, reduced infarct volume and reduced central IL-17A levels in the acute phase and attenuate post stroke cognitive impairment in the chronic phase. However, it is not known whether elevated central IL-17A signaling alone is sufficient to drive cognitive impairment after stroke. Here, we examined the effects of intracerebroventricular (ICV) IL-17A administration on hippocampal neuroinflammation and cognitive function in middle-aged female rats.Middle-aged female Sprague-Dawley rats (9–12 months) received ICV injections of recombinant human IL-

17A. In an initial acute-phase study (5 days), animals received 0, 50, 100, or 200 ng IL-17A to determine the optimal dose for microglial activation in the hippocampus. Following dose selection (200 ng), a separate 30-day long-term study was conducted comparing vehicle (0 ng) and IL-17A (200 ng) groups to evaluate cognitive outcomes using the Barnes Maze (spatial memory) and Novel Object Recognition Test (NORT; recognition memory).Microglial activation, determined by immunohistochemistry for Iba1 and CD68 indicated that the 200ng dose of IL-17A significantly elevated the number of Iba1+/CD68+ microglia and was selected for behavioral studies. Despite robust microglial activation, IL-17A-treated animals showed no impairment in spatial learning or memory on the Barnes Maze. In NORT, both vehicle and IL-17A treated groups showed reduced discrimination indices; however, IL-17A-treated animals spent significantly less time exploring the novel object, indicating diminished exploratory drive rather than a memory deficit per se.These results indicate that central IL-17A signaling is sufficient to activate microglia but insufficient on its own to produce the cognitive deficits characteristic of post-stroke injury. This dissociation suggests that stroke-induced cognitive impairment likely requires a comprehensive neuroinflammatory environment, including the convergent actions of IL-17A, IL-6, and TNF-α, Current studies are evaluating whether targeted IL-17 pathway suppression following experimental stroke can attenuate chronic neuroinflammation and preserve cognitive function.

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Poster

PSTR354: Neuroinflammation: Disease Mechanisms

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Program #/Poster #: PSTR354.02/W23

Topic: B.09. Glial Mechanisms

Support: NIH R21 MH124294 grant
TMCF-Novartis faculty research award and Brain & Behavior Research Foundation young investigator award
NIH Temple University MiNDS program
HBMC-CZI grant (PI: Pamela Clarke)

Title: Investigation of the role of Iba1 protein in adult microglia during the neuroprotective phase of ischemic stroke

Authors: *R. BUSSEY;
Howard Univ. Col. of Med., Washington DC, DC

Abstract: Ischemic stroke results from reduced or transient loss of blood flow to the brain, leading to neuronal death. Currently, there is limited to no treatment options for stroke. Stroke triggers a complex inflammatory response involving microglia, the brain's resident immune cells. Microglia are activated within minutes following a stroke. Ionized calcium-binding adapter

molecule 1 (Iba1), encoded by the *Aif1* gene, is an intracellular, proinflammatory protein in microglia and macrophages and widely used as a microglial marker. Iba1 plays critical roles in membrane ruffling and phagocytosis in macrophages in vitro and facilitates production of IL-6 and TNFα. Using germline Iba1-deficient mice, our laboratory has shown that Iba1 is required for microglial branching complexity, and ATP-directed motility and for excitatory synaptic growth in the normal postnatal brain. However, its specific contributions to neuroprotection or neuroinflammation following stroke during adulthood remain unclear. This study investigates whether microglial-specific loss of Iba1 specifically during the adult stage, improves or worsens stroke outcomes. Using the photothrombotic lesion model in control (*TMEM119-CreER^{T2}/+* or *Aif1$^{Flox/Flox}$*) and Iba1 conditional knockout (*TMEM119CreER^{T2}/+; Aif1$^{Flox/Flox}$*) mice treated with tamoxifen at 2.5 months, we assessed infarct size at 24 hours post-injury, via serial tissue sectioning and Nissl staining. Immunohistochemistry and fluorescent microscopy were used to assess microglial survival, and when combined with Sholl analysis allowed quantification of changes in their branching complexity. Our findings will provide insight into Iba1's role in microglial activation post-stroke and advance our understanding of how microglial proinflammatory proteins contribute to neuroprotection, potentially informing therapeutic strategies targeting microglial function.

Disclosures: R. Bussey: None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.03/W24

Topic: B.09. Glial Mechanisms

Support: 100332977-UALVIEP/24-1
Conahcyt 4024716

Title: Region-Specific Glial Reactivity and Cognitive Decline in a Rat Model of Type 2 Diabetes and Obesity

Authors: *A. M. COSS-OROZCO[1,2], B. M. SANCHEZ[2], R. A. VAZQUEZ-ROQUE[2];
[2]Inst. of Physiol., [1]Meritorious Autonomous Univ. of Puebla (BUAP), Puebla, Mexico

Abstract: Diabetes is a chronic metabolic disorder frequently comorbid with obesity, and together these conditions synergistically drive central nervous system pathology. Type 2 Diabetes (T2D) is characterized by pancreatic β-cell failure, peripheral insulin resistance, and sustained hyperglycemia which, alongside obesity-driven systemic inflammation, converges on a shared outcome: neuroinflammation, gliosis, oxidative stress, mitochondrial dysfunction, and blood-brain barrier disruption. Both conditions independently promote microglial activation and astrocyte reactivity in the hippocampus and prefrontal cortex, regions critical for memory and executive function. The resulting glial reactivity disrupts synaptic integrity, inhibits

neurogenesis, and promotes neuronal loss, collectively giving rise to the cognitive impairment described as "diabetic encephalopathy", a complication increasingly recognized as inseparable from its metabolic complications at large.
In this study we investigated how hyperglycemia and obesity affect glial activation, and how it correlates with inflammation, and oxidative stress regulation markers in a model of T2D (Zucker Diabetic Fatty rat). For this purpose, we used a combination of immunofluorescent probes in the Hippocampal region (Dentate Gyrus, CA1, and CA3) and Prefrontal Cortex (Prelimbic Cx ,PL, and Infralimbic Cx, IL) of Lean ZDF and Hyperglycemic Obese ZDF rats (n = 6, for each group) of 13 weeks of age. Our results demonstrate a differential expression of astrocyte, microglial, inflammation, and oxidative stress markers (GFAP, Iba1, COX2 and Nrf2) in comparison to the control, as well as an apparent change in morphology in microglia in both HIP and PFCx. Memory integration was measured via the Object-Place-Context test, and the diabetic group was found impaired in the integration phase. Motor activity was measured as well, and found to be decreased in the diabetic group.
These results are consistent with findings of a decrease in neuron density, atrophies in neuron morphology, as well as inflammation and oxidative stress markers reported previously by our lab and in the literature in the diabetic brain. These findings suggest a bidirectional relationship that supports the mechanisms behind diabetic encephalopathy.

Disclosures: A.M. Coss-Orozco: None. **B.M. Sanchez:** None. **R.A. Vazquez-Roque:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.04/W25

Topic: I.09. Spatial Navigation

Support: Departamento de Ciencias de la Salud

Title: From inflammation to Neurotoxicity: hypercaloric diet and quinolinic acid as risk factors for spatial memory alterations

Authors: *K. R. ALVA-ANDRADE[1], P. TORRES GARCÍA[2], K. R. GUZMAN-RAMOS[3]; [1]Biol. and Hlth. Sci., Univ. Autónoma Metropolitana-Unidad Lerma, City Toluca, Mexico; [2]Biol. and Hlth. Sci., Univ. Autónoma Metropolitana, Lerma de Villada, Mexico; [3]Biol. and Hlth. Sci., Univ. Autónoma Metropolitana, Lerma, Mexico

Abstract: Hypercaloric diets (HFD) represent a public health problem in Mexico due to their association with obesity, metabolic alterations, and chronic low-grade inflammation. These conditions not only affect physical health but may also compromise cognitive functions such as spatial memory. Among the possible mechanisms involved, the production of neuroactive metabolites derived from inflammatory processes stands out, including quinolinic acid (QA), which has been associated with neurotoxicity, alterations in neuronal plasticity, and cognitive

impairment. It is important to mention that hypercaloric diet and QA have been associated as risk factors for the development of neuropsychiatric and neurodegenerative diseases, as well as neuropsychological alterations. Understanding this interaction is relevant for identifying early mechanisms of brain vulnerability associated with unhealthy lifestyles. The objective of this study was to develop and characterize an experimental model of mild cognitive alteration that allows the evaluation of the interaction between hypercaloric diet and quinolinic acid on spatial memory, with emphasis on its relevance to brain health. Based on the above, C57BL/6 mice (~12 weeks old) were assigned to normal chow-saline and HFD-QA groups. Spatial memory was evaluated in the Morris Water Maze using conventional measures as well as in-depth spatiotemporal behavioral metrics. In addition, hippocampal correlates associated with neuroinflammation and tissue damage were analyzed using GFAP, IBA-1, and Nissl staining. The HFD-QA combination was associated with alterations in spatial memory performance, accompanied by changes in inflammatory markers and neurotoxicity at the hippocampal level. These findings suggest that the interaction between metabolic and inflammatory factors may promote a state of brain vulnerability with behavioral consequences. In conclusion, this model provides preclinical evidence of how factors linked to metabolic and inflammatory health may converge to affect cognitive function. Its value lies in offering a translational approach to studying early risk mechanisms, as well as potential targets for prevention and intervention aimed at protecting brain health.

Disclosures: K.R. Alva-Andrade: None. **P. Torres García:** None. **K.R. Guzman-Ramos:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR354.05/W26

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NIA ViCTER RO1ES033462-01
NIH 1R21NS118224-01

Title: RGS10 IS REQUIRED FOR THE METABOLIC AND NEUROINFLAMMATORY BENEFITS OF NLRP3 DEFICIENCY IN DIET-INDUCED METABOLIC DYSFUNCTION

Authors: *D. J. GRESHAM[1], J. BYUN[1], J. CHUNG[1], A. ADEBOWALE[1], J. LIM[1], N. DIEP[1], J.-K. LEE[1], M. C. HAVRDA[2];
[1]Physiol. and Pharmacol., Univ. of Georgia, Athens, GA; [2]Biomed. Sci., Univ. of New England, Portland, ME

Abstract: Chronic low-grade inflammation is a central driver of obesity, metabolic disorders, and neurodegenerative diseases. The NLRP3 inflammasome is a key mediator of inflammatory signaling in immune and metabolic tissues, yet the upstream mechanism remains incompletely

defined. Regulator of G-protein signaling 10 (RGS10) is a homeostatic protein in microglia and a negative regulator of myeloid cell activation. Here, we investigated how RGS10 controls NLRP3 inflammasome signaling and its consequences for peripheral metabolism and hypothalamic inflammation, using complementary *in vitro* and *in vivo* models. In bone marrow-derived macrophages, loss of RGS10 amplified NLRP3 signaling during both priming and activation in a calcium-dependent manner, increasing NLRP3, pro-IL-1β, and pro-GSDMD expression, as well as caspase-1 cleavage and IL-1β maturation and secretion. *In vivo*, *Nlrp3*$^{-/-}$ mice fed a high-fat diet (HFD) exhibited reduced weight gain, improved glucose tolerance and insulin sensitivity, decreased hepatic steatosis, and reduced inflammatory gene expression in liver and adipose tissue, whereas *Rgs10*$^{-/-}$ *mice* displayed the opposite phenotype, with exacerbated weight gain, impaired glucose homeostasis, and increased hepatic and adipose inflammation. This metabolic protection was substantially attenuated in double knockout (DKO; *Nlrp3*$^{-/-}$/*Rgs10*$^{-/-}$) mice, revealing a previously unrecognized functional interaction in which RGS10 is required for the full metabolic benefit of NLRP3 deficiency. We next extended our analysis to the CNS, where HFD-induced hypothalamic neuroinflammation showed region-specific dependence on RGS10. In the arcuate nucleus (ARC), NLRP3 deficiency reduced both IBA1 and GFAP levels, an effect that was abolished in DKO mice. In the dorsomedial hypothalamus (DMH), by contrast, both *Nlrp3*$^{-/-}$ and DKO mice showed reduced IBA1 and GFAP, indicating that this reduction occurs independently of RGS10. Together, these findings identify RGS10 as a critical, region-specific upstream regulator of NLRP3-dependent inflammation in the periphery and the CNS and demonstrate that RGS10 is required for the metabolic and neuroinflammatory benefits of NLRP3 inhibition in diet-induced metabolic dysfunction.

Disclosures: D.J. Gresham: None. **J. Byun:** None. **J. Chung:** None. **A. Adebowale:** None. **J. Lim:** None. **N. Diep:** None. **J. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Founder of NeuronityTx Inc.. **M.C. Havrda:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR354.06/W27

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NIGMS P20AGM109091-10S3
R21DA058586

Title: Alteration of Microglial Health and Inflammatory Memory by Antiretrovirals in a BV2 Cell Culture Model

Authors: *M. A. WALKER[1], H. JI[2], H. LI[1], R. M. BOOZE[1], C. F. MACTUTUS[1], M. SHTUTMAN[2];

[1]Dept. of Psychology, [2]Drug Discovery and Biomed. Sci., Univ. of South Carolina, Columbia, SC

Abstract: Despite the effectiveness of combination antiretroviral therapy (cART), HIV-associated neurocognitive disorder (HAND) still occurs in up to 50% of people living with HIV (PLWH). Additionally, research has begun to reveal ways cART may disrupt the normal functioning of microglia in these individuals. Given the lifelong commitment required of cART treatment, it is crucial to study any neurotoxic effects this treatment regimen may have that accumulate over time. To better understand how cART may impede the health of microglia, the present study observed how two frontline cART regimens impacted cell viability *in vitro*, and how this cell viability may be linked to other biological processes. BV2 cells (immortalized murine microglia) were treated with either BIC/FTC/TAF or FTC/TFV/DTG for 6, 12, 24, and 48 hours. Total and live cell counts were then obtained using the BioRad TC20 Automated Cell Counter. Neither cART model had a significant impact on live cell count overall. Over time, both cART models had greater live cell counts compared to vehicle controls, though there was evidence that untreated cells' levels were higher as well. This indicates that the most apparent alterations to microglial function are better seen when viewing data with the additional context of time. These data were then compared to previous data on how the same treatment regimens impacted microglial metabolic activity and cytokine expression to assess if there were any correlations between any of the three processes. There were no significant correlations for either drug model. This suggests that the effects of cART on microglia may not be as broad as was hypothesized. The lack of correlations may also indicate abnormal microglial activity disproportional to live cell counts. The next phase of experimentation will begin to focus on whether antiretrovirals create a lasting inflammatory state in microglia that leads to persistent neuroinflammation as seen in PLWH on cART with HAND.

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Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.07/W28

Topic: I.08. Learning and Memory

Title: MICROGLIAL PHENOTYPE CHANGES INFLUENCED BY COLORED RICE IN MOUSE WITH MILD CEREBRAL HYPOPERFUSION

Authors: *D. WATTANAUMADECHAKUL[1,2], S. CHOMPOOPONG[3];
[1]Anat., Mahidol Univ., Thailand, Thailand; [2]Anat., Mahidol Univ., Bankok Noi, Thailand; [3]Dept. of Anatomy, Fac. of Med. Siriraj, Bangkok, Thailand

Abstract: Microglia are involved in brain development, while their activations are linked to a wide range of diseases, interest in microglial function has increased over the last decade. In mild cerebral hypoperfusion, microglia activation refers to profound changes in microglial morphology and mRNA marker. Hippocampus and basal forebrain including nucleus accumbens (NuAc) and nucleus basalis of Meynert (NBM) are susceptible to ischemic damage and affect cognitive functions. Colored rice including black glutinous (BR) and riceberry rice (RR) is more nutrients than white rice (WR). Particularly, anthocyanin in colored rice improves condition of high cholesterol, diabetes, and cognition. To investigate whether colored rice influences microglial phenotype changes caused by mild cerebral hypoperfusion. Modified bilateral common carotid artery occlusion (mBCCAo) in sixty male mice, pre-treatment (10 days) and post-treatment (5 days) of RR and BR compared with WR was performed at 12 mg/kg orally. Pro-inflammatory and anti-inflammatory types of microglia activation are two general phenotypes, their regulation is crucial to neuroinflammatory response. The occlusion groups showed higher iNos, CD32 and CCL2 mRNA expression than sham group. RR group showed lower iNos, CD32 and CCL2 mRNA levels significantly at $p < 0.1$, $p < 0.05$ and $p < 0.05$, respectively. In contrast, BR group showed the highest CD206, AG-1 and YM-1 mRNA levels. Therefore, mBCCAo exhibited increased pro-inflammatory type of microglia activation leading to memory impairment. Both RR and BR may ameliorate with increasing anti-inflammatory types of microglia activation and ChAT expression. In addition, increased percentage of neuronal cell death in NuAc and NBM was related to memory deficits in a Morris water maze and trace fear conditioning tests. While cell death in those regions in RR and BR group significantly decreased and ERK1/2 related to long term memory potential (LTP) show significantly increased with compared to occlusion group. RR and BR also increased ChAT expression in NuAc and NBM. BR also significantly attenuated microglia activation indicated by Iba1 staining in hippocampus. BR and RR could attenuate white matter damage by increasing amount of myelin basic protein. In contrast, WR and BR could decrease TNF-α and IL-1β than RR, while BR increase IL-10 in serum and brain. Based on research findings, colored rice, BR shows anti-inflammatory types of microglia activation and more neuroprotective property against arterial occlusion in mice. The result aligns with evidence suggesting that neurological patients may have benefit of consuming colored rice instead of white rice daily.

Disclosures: D. Wattanaumadechakul: None. **S. Chompoopong:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.08/W29

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: This research was supported by the Division of Translational Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health, and Human Services ZIA ES103387-02.

Title: Neuroimmune dysregulation as a potential contributor to neurotoxicity of environmental fungicides

Authors: *A. MISHRA, D. KENDRICKS, G. J. HARRY, C. MCPHERSON;
Mechanistic Toxicology Br., Natl. Inst. of Envrn. Hlth. Sci., Durham, NC

Abstract: While *de novo* gene mutations can underlie neurological disorders, the potential contribution of environmental factors is becoming of increasing concern with a need to identify those with the greatest potential to harm the nervous system. These efforts led to large scale screening of cells in culture and assessments in alternative animal models. One such effort identified a group of chemicals that produced a transcriptional signature in cortical neurons defined by increased expression of neuroimmune genes and reduced expression of synaptic genes, often observed in neurodevelopmental and neurodegenerative disorders (Pearson et al., 2016). This group included the strobilurins, agricultural fungicides which target cytochrome b in mitochondrial complex III, with reports of developmental and reproductive impairments. Some indications of neurotoxicity have been reported in *in-vitro* screening systems. Based on the neuroimmune transcriptional signature, we examined exposure-related effects of two prominent compounds, azoxystrobin and trifloxystrobin, as they relate to alterations in brain microglia function. At exposure levels insufficient to affect mitochondrial bioenergetics, BV2 microglia displayed no direct induction of an inflammatory response yet a dysregulation of the inflammatory response induced by lipopolysaccharide (LPS). This was characterized by selective inhibition of LPS-induced elevation of *Il1a, Il1b* and *Il6* with trifloxystrobin, that was not seen with azoxystrobin. No alteration was observed in non-inflammatory phagocytic functions of microglia. The disruption of a normal immune macrophage response to challenge may reflect an alteration in a critical cellular component required for nervous system development and in maintaining homeostatic balance.This research was supported by the Division of Translational Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health, and Human Services ZIA ES103387-02.

Disclosures: A. Mishra: None. **D. Kendricks:** None. **G.J. Harry:** None. **C. mcpherson:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

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Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: SECIHTI Mexican PhD grant CVU 1076906

Title: Effects of Methylmercury, lead and their mixtures on IL-6 secretion in HMC-3 cells

Authors: *E. F. RAMIREZ, L. C. HERNANDEZ, A. ORTEGA, E. CALDERON-ARANDA;
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Abstract: Heavy metals such as lead (Pb) and methylmercury (MeHg) are potent neurotoxicants, causing calcium disruption, depletion of thiol groups, and inducing inflammation. Exposure to Pb and MeHg above their permissive concentrations results in neuroinflammation due to the activation of microglia, nevertheless, adverse effects are also present after the exposure to Pb and Hg low concentrations. One of the inflammatory factors affected is IL-6, a pleiotropic cytokine involved in inflammation but also in cellular homeostasis and specifically in neurodevelopment, which is a vulnerable stage in which heavy metals are lethal. In nature, all the elements are found forming mixtures, so the interactions and effects are different when experimentally analyzed separately; therefore, studying the effects of mixtures is a task of great relevance. In this context, our aim was evaluate the effect of Pb and MeHg exposure either separately or in mixture on IL-6 secretion pattern in a human microglia cell line. To this end, the HMC-3 cell line of human microglia was cultured, exposed for 48 and 72 h to IFN-g (50 ng/ml) with LPS (100 ng/ml) and to Pb and/or Hg concentrations below or equal to the permissible limits in the blood of pregnant women and children. For Pb (NOM-199-SSA1-2000: 5 ug/dl/PbB) 210 and 21 nM and for Hg (NRC 2001: 3.5 ug/HgB), 10 and 100nM. We first evaluated cell viability with WST-8 and then used an ELISA assay; we established the IL-6 secretion levels in supernatants of the referred treatments. As expected, none of the treatments decreased cell viability at 48 or 72 h of exposure. Interestingly, IL-6 secretion was increased only by the exposure to 100 nM MeHg at 48h; however, at 72h, there was no effect. The concentration of 10 nM MeHg did not affect IL-6 secretion, nor did treatments with Pb 21 or 210 nM at 48 or 72h. In sharp contrast, exposing microglia to mixtures of Pb with MeHg, the IL-6 secretion effect of 100 nM MeHg with was almost completely prevented. These results reveal the complexity of the study of the exposure to metal mixtures, nevertheless, their study is compulsory for a much needed understanding and characterization of the neurotoxic mechanism triggered by the so-called safe levels of these metals in the blood of pregnant women and children.

Disclosures: E.F. Ramirez: None. **L.C. Hernandez:** None. **A. Ortega:** None. **E. Calderon-Aranda:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.10/X1

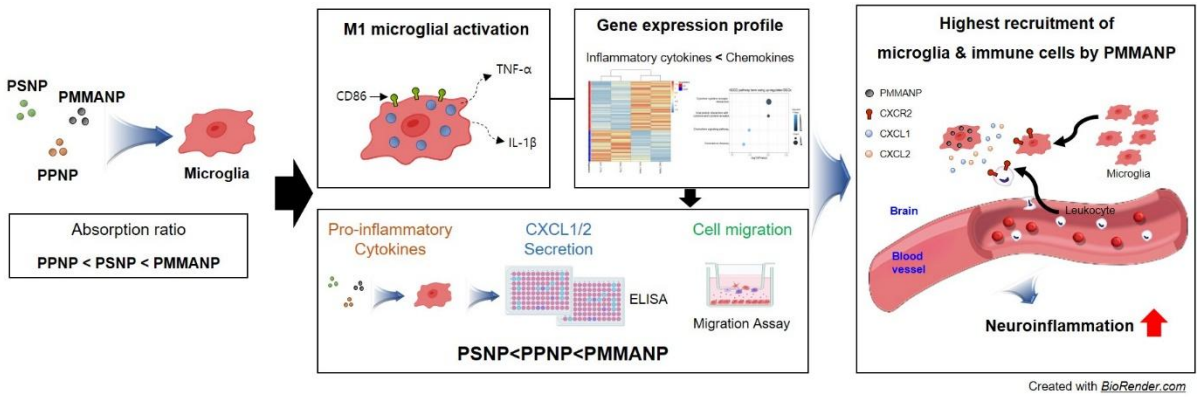
Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: KGM5362521
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CAP20024-002

Title: Type-dependent effects of nanoplastics on microglial activation and CXCR2-mediated chemotactic migration

Authors: ***J. KOO**[1,3], B. JEONG[4], J. BAEK[2], S. PARK[2], S. KIM[5], D.-Y. LEE[6]; [2]Biotherapeutics Translational Res. Ctr., [1]Korea Res. Inst. of Biosci. and Biotech., Daejeon, Korea, Republic of; [3]Korea Univ. of Sci. and Technology(UST), Daejeon, Korea, Republic of; [4]Developmental Neurobio., St. Jude Children's Res. Hosp., Memphis, TN; [5]Sch. of Life Sci. & Biotech., Kyungpook Natl. Univ., Daegu, Korea, Republic of; [6]Biotherapeutics Translational Res. Ctr., Korea Res. Inst. of Biosci. and Biotech, Daejeon, Korea, Republic of

Abstract: As plastic pollution continues to grow in various ecosystems, potential harmful effects of micro- and nanoplastics have become a great concern. Most studies on the biological effects of nanoplastics have been conducted using polystyrene nano- and microplastics. However, the majority of environmental plastic waste consists of a mixture of various types of plastics, such as polypropylene (PP), polyethylene, polystyrene (PS), polyvinyl chloride and polymethyl methacrylate (PMMA). In this study, we compared the biological effects of nanoplastics derived from three different types of plastics (PS, PP and PMMA) on the functions of microglia, which are the predominant immune cells with macrophage-like functions in the brain. Our experiments with cultured primary rat microglia revealed that the cells exposed to PMMA nanoplastic (PMMANP) exhibited the highest M1 phase activity. In addition, we found that PMMANP increased the migration ability of microglia by inducing the expression of chemokines, such as CXCL1 and CXCL2, in vitro and in vivo. These findings suggest that PMMANP-exposed brain microglia may accelerate neurological disorders by enhancing the recruitment of microglia and peripheral immune cells across the blood-brain barrier under neuropathological conditions.



Disclosures: J. Koo: None. **B. Jeong:** None. **J. Baek:** None. **S. park:** None. **S. Kim:** None. **D. Lee:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

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Program #/Poster #: PSTR354.11/X2

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NICHD R01HD108015 (Manuzak)
NIH/OD R21OD031435 (Manuzak)
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Title: A Single Episode of Malaria Elicits Hippocampal Neuroinflammation and Microglia Activation but not Astrocytosis in Pregnant Rhesus Macaques

Authors: *J. PRUSAK, Jr[1,4], S. FELL[1,4], H. GREEN[1], S. M. NEMPHOS[5], A. RODGERS[2], J. PERRET[2], C. MIDKIFF[2], L. DOYLE-MEYERS[3], A. MACLEAN[2,6,7,4], B. LONDONO[8], J. MANUZAK[1,4,8];
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Abstract: Introduction: Pregnancy is a period characterized by extensive adaptations to maternal immunological and organ systems. The brain adapts to pregnancy with regional alterations to gray matter volume, immunological suppression, and microglia density. These alterations may leave the brain vulnerable to damage from inflammation and infections. Utilizing the *Plasmodium fragile* model of malaria in pregnancy (MIP) in rhesus macaques, we examined the effects of MIP on blood-brain barrier tight junction (TJ) loss and glial cell activation throughout pregnancy. We hypothesized that *P. fragile* MIP would result in increased maternal neuroinflammation and vascular damage in brain regions shown to be altered during pregnancy.Methods:Pregnant RMs were inoculated with $20x10^6$ *P. fragile*-infected erythrocytes (n=9) or saline (n=9) during early- (gestational day [G]28, (*n*=3)), mid- (G65, *n*=3), and late-pregnancy (G100, *n*=3) followed by necropsy ~4 weeks post-inoculation (p.i.). Parasitemia was monitored by Giemsa-staining of thin blood smears. Quinine sulfate was administered when parasitemia exceeded 0.5%. At necropsy, RMs were perfused with 1x PBS and maternal brain was sectioned, fixed in 2% paraformaldehyde, and embedded in optimum cutting temperature compound. Tissue sections from brain regions altered by pregnancy including the frontal lobe, hippocampus (HPC), basal ganglia, and cerebellum were assessed for TJ loss (Zo-1, glut-1), astrocyte activation (GFAP), and microglia frequency (Iba1) and counterstained with DAPI. Astrocyte and microglia morphology was measured utilizing MBF's Neuroleucida software.Results:Peak parasitemia was observed by day 12 p.i. (median=13.29%; range=13.01-57.50%). In the HPC, as compared to controls, RMs with *P. fragile* MIP had significantly decreased TJ integrity (p=0.0464) and increased microglia density (p=0.0142), with no observed differences in astrocyte activation. We found that microglia had deramified morphology in the HPC with decreased Sholl arbor length area under the curve (AUC) (p=0.0025) and arbor nodes AUC (p=0.0016). We did not observe evidence of TJ loss or glial cell activation in the frontal lobe, basal ganglia, or cerebellum.Conclusions:These data suggest that, of the brain regions altered by pregnancy, the HPC may be more vulnerable to TJ loss and neuroinflammation from *P. fragile* malaria. We did not observe astrocytosis, which may be due to the quinine sulfate controlling parasitemia, thereby limiting neuroinflammation. Our future directions include

correlating these findings with perturbed neuroimmune factors in matched cerebrospinal fluid and peripheral factors.

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Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR354.12/X3

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant U54 NS060659
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Title: Neuregulin-1 Selectively Modulates Inflammatory Signaling and Survival Pathways in Activated Microglia

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Abstract: Background: Neuregulin-1 (NRG-1) is an endogenous growth factor with demonstrated neuroprotective and anti-inflammatory effects in models of central nervous system injury. However, the mechanisms by which NRG-1 regulates microglial activation remain incompletely understood.Methods: SIM-A9 microglia were treated with lipopolysaccharide (LPS; 1 μg/mL), interleukin-4 (IL-4; 50 ng/mL), and NRG-1 (10-100 ng/mL) alone or in combination. Nitric oxide (NO) production, IL-6 secretion, and expression of ErbB4 and Arginase-1 were assessed using Griess assay, ELISA, and Western blotting. Global transcriptional responses were evaluated using NanoString Inflammation (248 genes) and Neuropathology (757 genes) panels.Results: SIM-A9 microglia constitutively expressed the ErbB4 receptor, and NRG-1 treatment increased the membrane-associated ErbB4 cleavage fragment, confirming receptor activation. Unlike IL-4, NRG-1 did not induce Arginase-1 expression and produced minimal effects on LPS-induced NO and IL-6 production. Transcriptomic analysis revealed that NRG-1 altered 41 genes in unstimulated microglia compared with 154 genes altered by LPS and 85 genes altered by IL-4. In LPS-stimulated cells, NRG-1 reversed only a subset of inflammatory gene changes and produced a distinct transcriptional profile. Pathway analysis identified modulation of NF-κB and apoptosis signaling as major NRG-1-responsive pathways. NRG-1 reduced expression of canonical inflammatory mediators, including Traf6, while increasing expression of non-canonical NF-κB pathway

components, including RelB, Nfkb2 (p100), and Chuk (IKKα), as well as genes associated with cell survival. NRG-1 also increased expression of Cd33, a marker associated with immune regulation and inflammatory resolution.Conclusions: NRG-1 does not promote a classical anti-inflammatory microglial phenotype. Instead, it selectively reshapes inflammatory signaling by enhancing non-canonical NF-κB and survival pathways while preserving aspects of the innate immune response. These findings identify a distinct immunomodulatory mechanism through which NRG-1 may contribute to neuroprotection and resolution of neuroinflammation.

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Poster

PSTR354: Neuroinflammation: Disease Mechanisms

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Program #/Poster #: PSTR354.13/X4

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Sleep fragmentation alters microglial function leading to lethal neuroinflammation during sepsis-like inflammation

Authors: *A. WANI;
St. Jude Children's Res. Hosp., Memphis, TN

Abstract: It is well established that infection can promote slow wave sleep, but the functional importance of this phenomenon remains unclear. In this study, we utilized sleep fragmentation, i.e., intermittent disruption of sleep throughout the day, to explore the relationships between sleep and inflammatory disease. We found that sub-lethal injection of a bacterial lipopolysaccharide (LPS), prior to sleep fragmentation (SF) invariably resulted in dramatically increased mortality compared to LPS only or SF only controls, highlighting the importance of sleep following an inflammatory challenge. Further investigation revealed hyperactivation of microglia in the hypothalamus and other brain areas in mice subjected to LPS plus sleep fragmentation. As Toll-like receptor-4 (TLR4) is crucial for responses to LPS, we examined animals with microglia-specific deletion of TLR4 and found that it completely protected mice from the combination treatment. To further explore the role of sleep, we generated Dec2 (BHLHE41) mutant mice that display decreased sleep and found that these animals are protected from low dose LPS plus SF. We are currently extending our results to bacterial infection.

Disclosures: A. Wani: None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.14/X5

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: IL-13-mediated STAT6 signalling promotes anti-inflammatory microglial polarisation and enhances BDNF expression during neuroinflammation

Authors: *D. C. AJONIJEBU;
Human Anat. and Physiol., Univ. of Johannesburg, Johannesburg, South Africa

Abstract: Neuroinflammation is a common feature of neurological disorders and is driven by microglial activation, which can result in either a pro-inflammatory M1 phenotype associated with neuronal damage or an anti-inflammatory M2 phenotype that promotes neuroprotection. While IL-4 is known to induce M2 polarisation through STAT6 signalling, the role of IL-13 in regulating this pathway remains incompletely understood. This study investigated the role of IL-13 in regulating microglial polarisation and neuroprotective responses during LPS-induced neuroinflammation. C8-B4 microglial cells were stimulated with LPS to induce an M1 phenotype or treated with IL-4 and/or IL-13 to promote M2 polarisation. Cell viability was assessed following cytokine exposure. Pro-inflammatory (TNF-α, IL-1β) and neuroprotective (BDNF) protein levels were quantified using ELISA. Immunofluorescence analysis was used to evaluate the expression of microglial markers (Iba-1, CD86, CD206) and STAT6. Gene expression analyses of TNF-α, IL-1β, Arg-1, CD206, IL-4Rα, STAT6, and BDNF were performed using quantitative RT-PCR.LPS robustly induced a pro-inflammatory M1 microglial phenotype characterized by increased inflammatory marker expression. In contrast, IL-4 and IL-13 promoted alternative M2 polarisation and significantly enhanced the expression of anti-inflammatory markers. Both cytokines upregulated components of the IL-4Rα/STAT6 signalling pathway, supporting activation of downstream JAK/STAT signalling during inflammatory challenge. Notably, combined IL-4 and IL-13 treatment produced a synergistic increase in BDNF expression, suggesting enhanced neuroprotective capacity in response to inflammatory insults.These findings demonstrate that IL-13, together with IL-4, plays a critical role in regulating microglial phenotypic switching through STAT6-dependent signalling. Furthermore, IL-13-mediated enhancement of BDNF expression may represent an important mechanism underlying neuroprotection and the resolution of neuroinflammation. Targeting IL-13/STAT6 signalling may therefore offer a promising therapeutic strategy for neuroinflammatory disorders.

Disclosures: D.C. Ajonijebu: None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.15/X6

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Cultured astrocytes demonstrate non-coordinated expression of fibrinogen chains in response to proinflammatory stimuli

Authors: *M. J. CLAXTON[1], D. ABE[2], N. KVIRKVELIA[3], A. S. REGNIER-GOLANOV[4], E. V. GOLANOV[5], G. W. BRITZ[6];
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Abstract: Astrocytes are key mediators of central nervous system neuroinflammation and form the glia limitans covering the surface and pericapillary brain parenchyma. We investigated whether transcriptional response of normal human astrocytes (NHAs) to proinflammatory substances include fibrinogen (FBG) chains as acute phase positive reactants. NHAs (18-21 week old fetal tissue, Sciencell) were cultured in astrocyte basal media and exposed to either artificial cerebrospinal fluid (aCSF), known neuroinflammatory substances: lipopolysaccharides (LPS, 1µg/mL)/ kaolin (Ka, 250µg/ml), or co-incubation of one of these substances alongside the Toll-like receptor 4(TLR4) inhibitor TAK-242 (3µM). After 24-hour treatment, total RNA was isolated using TRIzol, purified, and reverse transcribed for quantitative PCR (qPCR) analysis. Gene expression was quantified using SYBR Green (Bio-Rad) to evaluate alterations in expression of relevant genes. Astrocyte activation markers ALDH1L1 (LPS,1.73±0.43 fold increase (FI), $p = 0.04$; Ka, 29 ±6 FI, $p = 0.01$), AQP4 (LPS, 1.6±0.6FI, $p = 0.04$; Ka, 26.7±7 FI, $p = 0.05$), and GFAP (LPS, 0.25±0.07 FI, $p = 0.01$) were upregulated. The cDNA of inflammatory genes, including multiple IL1β (LPS,1.25±0.35 FI, $p = 0.03$; Ka, 57±15 FI, $p = 0.04$) transcript variants and IL6 (LPS,1.68±0.4 FI, $p = 0.01$; Ka, 6.6±1.64 FI, $p = 0.02$), were also elevated, accompanied by increased expression of NFKB1 (LPS, 2.05±0.57 FI, $p = 0.00$; Ka, 4.5±1.16 FI, $p = 0.03$) and NFKB2 (LPS, 1.4±0.27 FI, $p = 0.01$; Ka, 2.6±0.54 FI, $p = 0.02$), indicating activation of acute phase response. Expression of FBG chains increased (FGA, LPS,9.5±5.06 FI, $p = 0.03$; FGB LPS, 0.21±0.05 FI, $p = 0.04$; Ka, 7.3±1.76 FI, $p = 0.04$,and FGG LPS, 0.64±0.19 FI, $p = 0.01$; Ka, 11±2.9 FI, $p = 0.02$) following stimulation, in line with our previous observation of increased expression of FBG chain transcripts in response proinflammatory stimuli. Both LPS and Ka elicited strong inflammatory and reactive astrocyte gene expression programs in NHAs, including significant induction of FBG chains transcripts. Co-incubation with LPS or Ka with TAK-242produced only mild fold reductions (FR) (IL6, Tak Ka, 4.2±0.8 FR, $p = 0.03$) of inflammatory marker gene expression, suggesting that TLR4 inhibition alone is insufficient to fully suppress astrocyte responses to these stimuli and that additional signaling pathways may contribute to the observed transcriptional changes. These findings provide insight into astrocyte-mediated neuroinflammatory responses and support further investigation into the role of locally expressed FBG chains and related pathways in CNS injury.

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Poster

PSTR354: Neuroinflammation: Disease Mechanisms

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Program #/Poster #: PSTR354.16/X7

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Alterations in Fibrinogen Expression in the Glia Limitans and Cerebrospinal Fluid Flow During Neuroinflammation

Authors: D. ABE[1], M. CLAXTON[2], N. KVIRKVELIA[3], A. S. REGNIER-GOLANOV[1], *E. V. GOLANOV[1], G. W. BRITZ[4];
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Abstract: Cerebrospinal fluid (CSF) plays a critical role in the maintenance of normal brain function. While circulating along the subarachnoid space (SAS), the perivascular space, and through the brain parenchyma, CSF removes waste products/toxins of brain activity. However, the mechanisms of CSF flow regulation are not fully understood. The SAS and the perivascular spaces are separated from the parenchyma by a layer of astroglial endfeet forming *glia limitans* superficialis and perivascularis, respectively. Previously, we have demonstrated that astroglia are capable of expressing fibrinogen (FBG) chains, most notably the gamma variant (FGG), which is in line with earlier observations of extrahepatic constitutive expression of FBG. Furthermore, we showed that following injection of kaolin, a substance known to induce neuroinflammation, there was a marked increase of FGG mRNA at the ventral brain surface. We hypothesize that inflammation associated increase in FBG/FBG chains expression by *glia limitans* superficialis and perivascularis can hinder the CSF flow to minimize the spread of harmful elements, including pathogens, along the SAS and the perivascular space. In C57BL/6 male mice, neuroinflammation was induced by intracisternal injection of either kaolin (n=15) or lipopolysaccharide (LPS) (n=7). Additionally, mice were injected with kaolin (n=5) or LPS (n=7) alongside a TLR4 inhibitor (TAK-242) to evaluate the effects of TLR4 inhibition on neuroinflammation. Immunohistochemistry (IHC) was used to explore FBG expression on the whole brain. Fluorescent microspheres were used to trace CSF movement through the cisterns and perivascular spaces. FBG deposition and microsphere distribution were assessed across multiple brain regions. FBG levels showed non-significant increase in the kaolin (1.8%) or LPS (5.9%) groups compared with artificial CSF (aCSF) controls. However, TAK-242 administration resulted in a reduction by 28.0% of FBG deposition in the TAK-242 group (p=0.003 vs aCSF). Microsphere distribution revealed a consistent reduction (by 53.6%) in the TAK-242 group across both dorsal and ventral sides compared with aCSF controls (p=0.021). TAK-242 restored microsphere distribution especially in the dorsal and anterior regions in the LPS injected mice. We conclude that TLR4 modulates CSF dynamics not only through changes in FBG deposition. Baseline injection-associated conditions may already induce a proinflammatory reaction.

Disclosures: D. Abe: None. **M. Claxton:** None. **N. Kvirkvelia:** None. **A.S. Regnier-Golanov:** None. **E.V. Golanov:** None. **G.W. Britz:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

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Program #/Poster #: PSTR354.17/X8

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: The differential roles of the equilibrative nucleoside transporter-2 in glial phenotypes in the cortex and the hippocampus under LPS-induce neuroinflammation

Authors: *W. TSAI[1], T. CHU[2], K.-C. WU[3], C.-J. LIN[4];
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Abstract: Equilibrative nucleoside transporter-2 (Ent2) is one of the most widely expressed nucleoside transporters in the brain and plays an important role in maintaining nucleoside homeostasis and energy metabolism. Previous studies have shown that Ent2 deletion attenuates LPS-induced astrogliosis and microgliosis in both the cortex and hippocampus. In the present study, we further investigated the impact of Ent2 deletion on LPS-induced phenotypic changes of glia cells. ENT2$^{-/-}$ mice and littermate controls (Ent2$^{+/+}$) were subjected to 7 days of LPS treatment, glial phenotypes in the cortex and hippocampus were examined using immunofluorescence staining. In addition, C8D1A (astrocyte cell line) cultures were used to further explore astrocyte responses under LPS and ENT2 inhibition in vitro. In vivo, Ent2 deletion normalized LPS-induced M1/M2 microglial polarization in both the cortex and hippocampus. For astrocytes, the effects were more heterogeneous across brain regions: Ent2 deletion reduced LPS-induced A1 astrocyte activation in the cortex, while the effect was less pronounced in the hippocampus. In contrast, A2 astrocyte-associated signals were increased in both regions. In vitro, LPS directly induced A1 astrocyte activation in cell cultures, and pharmacological inhibition of Ent2 attenuated this response, consistent with the in vivo findings. These findings highlighting a region-specific role for Ent2 in regulating glial differentiation.

Disclosures: W. Tsai: None. **T. Chu:** None. **K. Wu:** None. **C. Lin:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

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Program #/Poster #: PSTR354.18/X9

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Serial time course assessment of lipopolysaccharide-induced neuroinflammation in the rat hippocampus using cerebral open flow microperfusion

Authors: C. SIMMONS, I. DAVIES, A. CHAND, L. WATKINS, S. BUTLER, N. BAXTER, N. MODY, P. PATNI, J. S. DAVIES, R. BRAMMER, D. RIAL, ***S. BÄCK**;
Sygnature Discovery, Nottingham, United Kingdom

Abstract: Neuroinflammation is implicated in neurodegenerative disorders, including Parkinson's and Alzheimer's disease, and may contribute to disease progression. Lipopolysaccharide (LPS) is widely used to model inflammatory responses in the brain. We previously evaluated LPS serotypes 055 and 0111 in male C57BL6/J mice and selected 055: B5 for follow-up in male Sprague Dawley rats, based on robust increases in proinflammatory brain biomarkers up to 24 h post-dose. However, these biomarkers were measured in postmortem tissue, limiting time-course interpretation. Each timepoint requires different animals, increasing variability and animal use, and residual peripheral biomarkers in brain vasculature may confound measurements despite perfusion.
Here we used cerebral open flow microperfusion (cOFM) to serially sample hippocampal interstitial fluid and generate a brain-specific time course of progranulin and cytokine changes after LPS challenge. Rats were implanted with two cOFM probes bilaterally in the dorsal hippocampus and recovered for 2 weeks. On the study day, the guide cannula dummy was replaced with a sampling insert, and animals were housed in microdialysis bowls with free access to food and water and unrestricted movement via a swivel system. Probes were left to stabilize for 2 h before sampling. Collections included a 4 h baseline and 12 h after LPS dosing at 1 h intervals. Progranulin was measured by ELISA and IL-1β, IL-6, TNF-α, and IFN-γ by MSD multiplex assay.
Progranulin and cytokines were easily detectable in all samples analysed. However, statistically significant increases were only detected in cytokine levels (IFN-γ and IL6 only) in the interstitial fluid from 4-12 h following the LPS challenge. These results demonstrate that the cOFM method enables serial measurement of inflammatory biomarkers within the same animal, providing higher resolution of the neuroinflammatory response for improved evaluation of therapies targeting neuroinflammation.

Disclosures: C. Simmons: A. Employment/Salary (full or part-time):; Sygnature Discovery. **I. Davies:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **A. Chand:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **L. Watkins:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **S. Butler:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **N. Baxter:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **N. Mody:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **P. Patni:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **J.S. Davies:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **R. Brammer:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **D. Rial:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **S. Bäck:** A. Employment/Salary (full or part-time):; Sygnature Discovery.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR354.19/X10

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NINDS R01 NS122777
NIH NIA R03 AG084940

Title: Mdivi-1 attenuates pro-inflammatory microglial NF-κB and HIF-1α signaling without preventing mitochondrial shortening

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Abstract: Mitochondrial fission in mammalian cells is mediated by dynamin-related protein 1 (DRP1). While mitochondrial division inhibitor 1 (mdivi-1) was originally described as a DRP1 inhibitor, it has since been shown to suppress pro-inflammatory activation in microglia. However, the mechanism underlying these effects remains unclear. Previous research has suggested a link between DRP1-dependent mitochondrial fragmentation and NF-κB-mediated pro-inflammatory signaling. We therefore hypothesized that mdivi-1 suppresses microglial pro-inflammatory activation by reducing NF-κB activity. Pro-inflammatory activation was modeled in mouse highly aggressively proliferating immortalized (HAPI) microglial cells treated with lipopolysaccharide (LPS) and interferon-gamma (IFNγ) ± mdivi-1. To determine whether suppression of the activation phenotype occurred downstream of mitochondrial fragmentation, mitochondrial morphology was assessed. While mdivi-1 reduced LPS/IFNγ-induced mitochondrial swelling, it did not restore the elongated, tubular morphology observed in vehicle-treated cells. These findings suggest that the anti-inflammatory effects of mdivi-1 are likely independent of mitochondrial fragmentation. We next investigated whether mdivi-1 modulates NF-κB dynamics. While mdivi-1 had no effect on NF-κB nuclear translocation following pro-inflammatory stimulation, it significantly reduced NF-κB-DNA-binding at 6 hours. Moreover, mdivi-1 suppressed NF-κB-dependent transcripts, including IL-1β, IL-6, and TNF-α, and reduced inducible nitric oxide synthase (iNOS) protein expression and nitric oxide release. Because NF-κB promotes the expression of hypoxia inducible factor 1α (HIF-1α), another transcription factor associated with the innate immune response, we next examined whether mdivi-1 affects HIF-1α. Mdivi-1 reduced both HIF-1α transcript and protein levels. Notably, this suppression occurred under conditions where nuclear NF-κB localization was not detected, suggesting that regulation of HIF-1α may occur independently of NF-κB. Stabilization of HIF-1α with dimethyloxalylglycine (DMOG) or deferoxamine mesylate (DFO) reversed the mdivi-1-mediated reduction in iNOS protein expression, indicating that inhibition of HIF-1α contributes to mdivi-1's anti-inflammatory effects. Together, these findings demonstrate that mdivi-1 attenuates microglial pro-inflammatory activation through at least two mechanisms: inhibition of NF-κB DNA-binding activity and reduction of HIF-1α expression.

Disclosures: D.D. Freeman: None. **R.P. Mayers:** None. **P. Rajagopal:** None. **S. Wilson:** None. **M. Karbowski:** None. **B.M. Polster:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.20/X11

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Time-dependent changes in glial reactivity and their relationship to behavioral alterations following olfactory bulbectomy in male rats

Authors: *M. BAUTISTA-CARRO[1,2], J. MORALES-MEDINA[2];
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Abstract: Anxious depression is characterized by the coexistence of a low mood and increased psychomotor activity, including hyperlocomotion. Glial abnormalities have been identified in the prefrontal cortex (PFC) of patients with major depression. Olfactory bulbectomy (OBX) is an animal model for studying agitated depression (anxious depression in humans). However, this model has been studied predominantly within the first 28 days following the lesion. Therefore, the glial changes that may precede the agitated depressive phenotype and whether they persist over long-term period remain unknown. We used 55 male Wistar rats (*Rattus norvegicus*) with OBX and sham lesions to determine the influence of postoperative time on locomotion and anxiety-like behaviors in the open field test. Immunohistochemistry was performed on PFC using glial fibrillary acidic protein and ionized calcium-binding adaptor molecule 1 to identify astrocytes and microglia, followed by cell counts and morphometric analyses. We found that OBX produces time-dependent behavioral and glial alterations. During a period of 7 and 28 days, OBX increased locomotion and anxiety-like behaviors, which are consistent with a psychomotor agitation phenotype. These behavioral alterations are accompanied by an increase in astrocyte density in both time periods, while microglial proliferation is detected only at 7 days in the PFC. This indicates an early neuroinflammatory response driven by microglia, followed by a more enduring astrocytic reactivity. In contrast, 105 days after the lesion, no behavioral changes or glial alterations are observed. The absence of behavioral and glial abnormalities during this period suggests that OBX acts as a transient model of agitated depression.

Disclosures: M. Bautista-Carro: None. **J. Morales-Medina:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.21/X12

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: RS-2025-25459402
RS-2025-16070516
BK21 R&E Initiative for Advanced Precision Medicine

Title: Neuron-microglial interactions in the facial motor nucleus drive spontaneous axon regeneration following facial nerve injury

Authors: *H. SEO[1,2,3], H. KIM[4,2], Y. SEO[7,3], J. YOON[5], S. JEE[9,2,3], B. JANG[8,3], S. SINGH[10,3], B. G. KIM[11,2,3,6];
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Abstract: Peripheral nervous system (PNS) neurons exhibit robust axonal regeneration after injury, unlike central nervous system (CNS) neurons. Recent studies indicate that interactions between neurons and non-neuronal cells play a significant role in promoting axonal regeneration after PNS injuries. We previously demonstrated that neuron-macrophage interactions promote axonal regeneration in dorsal root ganglia after sciatic nerve injury. However, it remains unclear whether microglial cells in the CNS can also contribute to axonal regeneration. To test the potential role of microglial cells in supporting axonal regeneration, we used a facial nerve injury (FNI) model in which facial motor neurons in the ventral brainstem exhibit an intrinsic capacity for spontaneous regenerative responses. Following a crush injury to the facial nerve main trunk, the number of microglial cells surrounding motor neurons in the facial motor nucleus (FMN) increased substantially. PLX5622, a CSF1R inhibitor, effectively reduced FMN microglia after FNI, accompanied by a significant delay in the recovery of functions assessed by eye closure and vibrissa movement. Retrograde tracing with FluoroGold injected into the whisker pad muscles showed an almost 50% decrease in the number of regenerating facial motor neurons, demonstrating that FMN microglia play a key role in spontaneous facial nerve regeneration. Single-nuclei RNA sequencing of the FMN region after FNI unexpectedly revealed upregulation of neuronal genes, including Tubb1, Map1b and Gap43, within the microglial population. The enrichment of neuronal genes was validated by bulk RNA-seq of FACS-isolated microglia from CX3CR1-GFP mice. Cell-to-cell interaction analysis is underway to identify ligand-receptor pairs that mediate neuronal gene enrichment in microglial cells. This study will provide insight into the mechanisms underlying the phenotypic switch that reprograms pro-regenerative microglial cells, ultimately revealing novel strategies for CNS regeneration.

Disclosures: H. Seo: None. **H. Kim:** None. **Y. Seo:** None. **J. Yoon:** None. **S. Jee:** None. **B. Jang:** None. **S. Singh:** None. **B.G. Kim:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.22/X13

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: CINVESTAV Funding

Title: Long-Term Mechanical and Cold Allodynia Following Olfactory Bulbectomy Occurs in the Absence of Hyperlocomotion and Is Associated With Basolateral Amygdala Glial Remodeling

Authors: *J. MORALES-MEDINA[1], M. BAUTISTA-CARRO[2,3], D. L. CORONA QUINTANILLA[4];
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Abstract: Olfactory bulbectomy (OBX) is a well-established rodent model that reproduces behavioral features associated with agitated depression; however, most studies evaluate outcomes within 3-4 weeks post-lesion. The present study examined long-term behavioral and glial alterations in the basolateral amygdala (BLA) at 15 weeks after OBX in male Wistar rats (*Rattus norvegicus*). Animals were assigned to two experimental cohorts. In the first, rats underwent OBX or sham surgery and remained undisturbed until assessment of exploratory behavior in the open-field test (OFT). In the second cohort, nociceptive sensitivity was evaluated weekly using mechanical and thermal assays. In the first cohort, OBX animals showed no significant changes in horizontal or vertical activity in the OFT but exhibited hypertrophic astrocytes in the BLA. In contrast, the nociceptive cohort developed persistent mechanical and cold allodynia without evidence of mechanical hyperalgesia. An increased number of astrocytes and the hypotrophic microglial morphology in the BLA accompanied these sensory alterations. Together, these findings indicate that OBX produces long-lasting glial remodeling and chronic pain-like states, supporting the neurobiological link between depression and pain comorbidity. Moreover, not all behavioral alterations occur at the same time as observed in depression.

Disclosures: J. Morales-Medina: None. **M. Bautista-Carro:** None. **D.L. Corona Quintanilla:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.23/X14

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIGMS R35 grant – NIH (JLW)

Title: Pain Hypersensitivity and Tissue-Specific Neuroimmune Alterations in a Letrozole-Induced Mouse Model of Polyendocrine Metabolic Ovarian Syndrome

Authors: *L. KHODAVIRDILOU[1], K. FRIMPONG-MANSON[1], B. OJO[2], J. WILKERSON[3]; [1]Rutgers, The State Univ. of New Jersey, Newark, NJ; [2]Rutgers Univ., Newark, NJ; [3]Dept. of Pharmaceut. Sci., Rutgers New Jersey Med. Sch., Newark, NJ

Abstract: Pain Hypersensitivity and Tissue-Specific Neuroimmune Alterations in a Letrozole-Induced Mouse Model of Polyendocrine Metabolic Ovarian Syndrome
Polyendocrine Metabolic Ovarian Syndrome (PMOS), formerly known as Polycystic Ovary Syndrome (PCOS), is the most common endocrine disorder in reproductive-aged women and is increasingly associated with pain-related symptoms. However, the mechanisms linking PMOS-like endocrine disruption to altered nociception remain poorly defined. This study evaluated whether chronic letrozole administration produces pain hypersensitivity and systemic and tissue-specific immune alterations in female mice. Adult female C57BL/6J mice (8-10 weeks old) received daily oral letrozole (1.78, 3.2, 5.6, or 10 mg/kg) or vehicle for 21 days. Estrous cyclicity was monitored by daily vaginal cytology, and pain-related behaviors were assessed at baseline and on days 1, 5, 10, 15, and 21 using the von Frey, hot plate, and acetone tests. Locomotor activity, plasma hormones, and multiplex cytokine profiles in plasma, dorsal root ganglia, spinal cord, prefrontal cortex, and hypothalamus were also evaluated. Letrozole disrupted estrous cyclicity, prolonged diestrus, and increased body and ovarian weight at higher doses. High-dose letrozole (10 mg/kg) increased circulating testosterone, supporting a hyperandrogenic PMOS-like phenotype. Letrozole produced dose- and time-dependent mechanical, cold, and thermal hypersensitivity, with the most sustained effects observed at moderate-to-high doses and no consistent locomotor impairment. Cytokine profiling showed that letrozole altered immune mediators differently across plasma and pain-relevant neural tissues. Plasma showed a mixed systemic immune response, whereas the spinal cord exhibited the broadest and most consistently upregulated immune profile. In contrast, the dorsal root ganglia and prefrontal cortex showed more restricted and predominantly reduced immune-recruitment or regulatory profiles, while the hypothalamus showed a selective cytokine response. Together, these findings demonstrate that letrozole-induced hyperandrogenism produces multimodal pain hypersensitivity accompanied by region-specific changes in neuroimmune signaling, with the spinal cord emerging as a major site of immune activation.

Disclosures: L. Khodavirdilou: None. **K. Frimpong-Manson:** None. **B. Ojo:** None. **J. Wilkerson:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.24/X15

Topic: I.09. Spatial Navigation

Title: Examining the effects of mild traumatic brain injury on cognitive measures and neuroinflammation in female and male rats

Authors: *V. MAASKANT[1], A. INOCENTES[1], A. MOFFATT[1], J. LEE[1], A. PIERCE[1], E. MOZALOVA[1], S. LUNA[1], M. KRAMER[1], J. B. HALES[2];
[2]Neuroscience, Cognition, and Behavior, [1]Univ. of San Diego, San Diego, CA

Abstract: Memories are central to understanding who we are, knowing where we came from, and planning for our future. A devastating consequence of traumatic brain injury (TBI) can be the loss or disruption of memory function. Although animal models of mild TBI (mTBI) can provide powerful tools for examining cognitive and behavioral symptomology and brain pathological changes, many do not accurately induce the types of brain impacts and injury that we see in humans. Our research uses the lateral impact procedure, developed to simulate the velocity, accelerations, and rotational forces associated with sports-related concussion or motor vehicle accidents (Viano et al., 2009). Historically, both human and animal studies of disease mechanisms have been limited to male subjects, creating a critical need for the inclusion of females and consideration of sex as a biological variable. In our study, we examined the effects of repeated mTBIs in male and female rats on memory, anxiety, locomotor, and spatial navigational functions. In addition, we examined neuroinflammatory responses through evaluation of microglial morphologies in the medial prefrontal cortex (mPFC), hippocampus, and medial entorhinal cortex. Preliminary results showed a sex by condition interaction in the percentage of hypertrophic microglia in the infralimbic area of the mPFC, with males who experienced repeated mTBIs showing the largest difference relative to their control group. In addition, we found marginally higher percentages of ramified microglia in both male and female control rats. By using a translatable animal model of mTBI and examining sex as a biological variable while evaluating the cognitive effects and neuroinflammation, we aim to build a more comprehensive understanding of brain injury pathology and support the development of more inclusive and effective treatments.

Disclosures: V. Maaskant: None. **A. Inocentes:** None. **A. Moffatt:** None. **J. Lee:** None. **A. Pierce:** None. **E. Mozalova:** None. **S. Luna:** None. **M. Kramer:** None. **J.B. Hales:** None.

Poster

PSTR354: Neuroinflammation: Disease Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.25/X16

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NIDCD grants R01 DC009405, R01 DC015792

Title: The time course of MHCII expression during neurodegeneration in the rodent cochlea after hair cell death

Authors: *Z. ZHANG[1], S. H. GREEN[2];
[2]Dept. of Biol., [1]Univ. of Iowa, Iowa City, IA

Abstract: In various models, the immune response has been shown to contribute to neurodegeneration. Thus, Investigations into neuron-immune interactions provide therapeutic possibilities for treating neurodegeneration. Spiral ganglion neurons (SGNs) receive auditory information from cochlear hair cells, the auditory receptor cells, and transmit it to the central nervous system. SGNs gradually degenerate following hair cell death. While an inflammatory immune response in the cochlea appears to be causal for neurodegeneration, it remains unclear which components of the immune response are responsible. Gene expression profiling shows dramatic upregulation of immune response-related genes, including the major histocompatibility complex (MHCII), a molecule involved in antigen presentation to lymphocytes and adaptive immune response, in the spiral ganglion following deafening. Preliminary data showed that the MHCII knockout prevents SGN degeneration, indicating a causal role for MHCII-mediated antigen presentation and the adaptive immune response in SGN loss. Here, we ask whether the timing of MHCII expression post-deafening correlates with the time course of SGN death in the mouse and rat models after hair cell loss. We demonstrated by immunolabeling that MHCII expression in both mouse and rat models appears to correlate temporally with SGN degeneration. In rats, immunohistology shows an increase in MHCII+ macrophages at P32, P39, P45 and P70. The significant SGN degeneration starts at P39 so our results show that post-deafening upregulation of MHCII occurs before SGN degeneration. In mice, at P13, P32 and P39, post-deafening SGN degeneration has not yet occurred and upregulation of MHCII expression is not apparent. At P60, SGN degeneration is apparent after hair cell loss as is increased MHCII expression. These results are consistent with a causal association between MHCII expression on spiral ganglion macrophages and SGN degeneration. The function of MHCII expression in this context remains to be elucidated.

Disclosures: Z. Zhang: None. **S.H. Green:** None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.01/X17

Topic: G.04. Neuroimmunology and Neurovirology

Support: The Swedish Cancer Society
The Swedish Research Council
The Swedish Brain Foundation
Sahlgrenska Academy

Title: A Neuroimmune Brainstem Pathway Selectively Drives Catabolism in Response to Viral Double-Stranded RNA Sensing

Authors: *F. FONT GIRONÈS;
Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Negative energy balance is a hallmark of systemic infection coordinated by the brain, yet how immune signals are translated into weight loss remains unclear. Here, we identify a principle whereby sensing of viral double-stranded (ds)RNA by toll-like receptor 3 (TLR3) induces a catabolic state through engagement of the area postrema (AP) and *nucleus tractus solitarius* (NTS). Using activity-dependent genetic trapping, we show that TLR3 activation recruits AP-NTS neurons to promote lipid mobilization. TLR3 signaling is required to elevate growth differentiation factor 15 (GDF15), which enforces catabolism independently of anorexia. Among diverse immune challenges, only TLR3 activation generates a catabolic response via $GFRAL^{+}$ neurons, the sole known target of GDF15. Brain-wide c-Fos mapping reveals that TLR3 and TLR4 agonists engage stimulus-specific areas, while activating a shared metabolic network. Together, these findings define a TLR3→GDF15→GFRAL axis selectively enforcing catabolism in response to viral dsRNA and a labelled-line-like organization of neuroimmune metabolic control.

Disclosures: F. Font Gironès: None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.02/X18

Topic: G.04. Neuroimmunology and Neurovirology

Support: 1R01NS148641-01
1R56NS138538-01

Title: Neuropathologic Interaction Between Viral Infection and Synucleinopathy

Authors: J. LI[1], X. TIAN[1], H. ZHANG[1], C. HAACKER[1], *X. LU[2];
[1]Pharmacology, Toxicology, & Neurosci., Louisiana State Univ. Hlth., Shreveport, LA; [2]LSU Hlth., Shreveport, LA

Abstract: Virus infections have been associated with chronic neurological and neurocognitive outcomes and late-onset neurodegenerative disorders (NDD). There are growing concerns regarding whether SARS-CoV-2 infection or other emerging viral infections could instigate and propagate neurological and cognitive sequelae (PASC) with the possibility of progressing to cognitive decline and dementia. To study the impact of virus infection on synucleinopathy in vivo, we generated a human ACE2 transgenic mouse model with full-length human ACE2 regulatory regions that faithfully recapitulated the structure, tissue distribution, and gene regulation of the human gene. SARS-CoV-2 infection in ABSL-3 facility established the feasibility of our model to study post-acute sequelae of COVID-19 (PASC) and age-dependent progression of neuropathology without drastic viral neuroinvasion and lethal encephalitis,

providing distinct advantages over the existing animal models. We further validated genotoxic stress and Lewy pathology phenotypes observed in mice using deceased COVID-19 and LBD patient brains. Finally, we found that inhibiting genotoxic stress can effectively lessen inflammation, cell senescence, accumulation of α-Synuclein, autophagy deficits, neuroinflammation, and cognitive and anosmia symptoms in an immunopathology model without viral neural invasion. ATM inhibition selectively in genotoxic stressed cells via a novel genetic strategy also rescued α-Synuclein aggregates spreading and cognitive deficits, suggesting a causal pathogenic role of genotoxic stress in synucleinopathy and long COVID symptoms. These data support that viral infection-driven brain genotoxic stress mediates the pathologic interaction between COVID-19 and synucneinopathy via perpetuating DDR/cell senescence, autophagy/lysosome acidification dysfunction, and neuroinflammation that sustains chronic cognitive and neurological deficits. The findings highlight the etiological role of viral infection in synucleinopathy.and advance the therapeutic targeting of genotoxic stress for PASCs and α-Syn pathology. Our study offers insights into the shared mechanisms between COVID-19/PASC and other chronic conditions with similar viral etiology and neurologic symptomatology, such as chemo brain, gulf war syndrome, and chronic fatigue syndrome.

Disclosures: J. Li: None. **X. Tian:** None. **H. Zhang:** None. **C. Haacker:** None. **X. Lu:** None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.03/X19

Topic: G.04. Neuroimmunology and Neurovirology

Support: NIH grant 3P51OD011104-62S2

Title: Insights into long-COVID and ADRD: Plasma metabolomic and proteomic analysis in SARS-COV-2 infected African green monkey.

Authors: *P. DATTA;
Tulane Univ., Covington, LA

Abstract: Background: Many reports indicate that SARS-CoV-2 infection causes central nervous system symptoms through inflammation, cerebrovascular effects, and viral neurotoxicity, resulting in long-term neurological issues. Our research seeks to understand the long-term changes in proteins and metabolites linked to the development of Alzheimer's disease and related dementias (ADRD) during SARS-CoV-2 infection, using an African Green Monkey non-human primate (NHP) model of Long COVID. Methods: SARS-CoV-2-infected African green monkeys, Chlorocebus aethiops sabaeus (n=10), were followed for 18 weeks during the natural course of infection. SARS-CoV-2 mRNA was quantified in nasal and pharyngeal swabs by qPCR. The Olink Target 96 Inflammation and Neurology proximity extension assay was used to assess changes in plasma proteins. Plasma metabolomic analysis was conducted using LC-MS.

Longitudinal comparisons were made from baseline through necropsy for specific protein markers and metabolites involved in the pathogenesis of ADRD. Results: Our proteomic analysis showed a significant increase in Delta/Notch-like EGF Repeat-Containing (DNER) protein and a significant decrease in neprilysin (NEP) at week 3 post-infection and at necropsy compared with baseline levels. Metabolite analysis revealed a significant decrease in 5-Hydroxyindole-3-acetic acid (5-HIAA) and an increase in 2-Oxindole at necropsy compared to baseline levels. Conclusions: Our research indicates that DNER, a neuron-specific transmembrane protein with extracellular EGF-like repeats that modulate Notch signaling, may contribute to the development of ADRD. Additionally, reduced levels of 5-HIAA, the end product of serotonin synthesis that influences Neprilysin, the primary enzyme responsible for degrading Aβ peptides, could lead to increased Amyloid-beta aggregation. Elevated levels of 2-oxindole, which can activate Aryl hydrocarbon receptor (AhR) signaling, compromise blood-brain barrier (BBB) integrity and worsen AD pathology.

Disclosures: P. Datta: A. Employment/Salary (full or part-time):; Tulane 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.; None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.04/X20

Topic: G.04. Neuroimmunology and Neurovirology

Title: Interaction of MTHFR deficiency and SARS-CoV-2 infection promotes Cerebrovascular and Parkinsonian pathology in mice

Authors: M. UMAR, S. ISMAEL, ***G. J. BIX**;
Tulane Univ., New Orleans, LA

Abstract: Objectives:
Methylene tetrahydrofolate reductase (MTHFR) regulates one-carbon metabolism and supports epigenetic processes and neurotransmitter synthesis, including dopamine. Common MTHFR variants (present in ~20-40% of the population) are associated with severe COVID-19, post-acute sequelae, cerebrovascular dysfunction, and Parkinson's disease. We investigated whether Mthfr deficiency in mice increases vulnerability to acute SARS-CoV-2-induced neurovascular and dopaminergic injury. **Methods:**
Ten-month-old *Mthfr*$^{+/-}$ and wild-type mice were intranasally infected with 10^4 PFU of mouse-adapted SARS-CoV-2 (MA10) or mock. Animals were sacrificed at 3 days post-infection. Lung and brain tissues were analyzed for viral load, blood-brain barrier (BBB) integrity, inflammatory markers, and dopaminergic pathway changes using qPCR and immunohistochemistry. Plasma metabolomics was performed to assess systemic metabolic alterations. **Results:**

Lung viral titers were comparable between wild-type infected and *Mthfr*$^{+/-}$ infected mice, and no viral RNA was detected in their brain tissue. *Mthfr*$^{+/-}$ mice following MA10 infection showed significant BBB disruption, including reduced tight junction protein ZO-1 expression and increased cortical vascular leakage. These changes were associated with elevated IL-1β mRNA expression, increased microglial count, and enhanced caspase-1 immunostaining. Metabolomic profiling identified dopamine as the most significantly reduced circulating metabolite in infected *Mthfr*$^{+/-}$ mice. In addition, MA10-infected *Mthfr*$^{+/-}$ mice exhibited Parkinsonian-like changes, including reduced tyrosine hydroxylase intensity, loss of dopaminergic neurons, decreased dopamine D1 receptor levels, increased α-synuclein intensity and higher microglial count in the substantia nigra. **Conclusions:**
SARS-CoV-2 infection causes BBB disruption, neuroinflammation, systemic dopamine depletion, and nigrostriatal dopaminergic degeneration in the context of MTHFR deficiency, even without detectable virus in the brain. These findings suggest that Mthfr deficiency may heighten susceptibility to post-COVID cerebrovascular and Parkinsonian-like pathology.

Disclosures: M. Umar: None. **S. Ismael:** None. **G.J. Bix:** None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.05/X21

Topic: G.04. Neuroimmunology and Neurovirology

Support: NIH Grant DC020980

Title: Genetic dissection of acute and long-term anosmia following SARS-CoV-2 infection

Authors: *M. XU;
Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Infection of the olfactory epithelium (OE) in COVID-19 patients is thought to underlie loss of smell (anosmia), a pathognomonic symptom that can be long-term in some patients, significantly affecting quality of life. The olfactory epithelium is also believed to be a major entry point for systemic SARS-CoV-2 infection, which can result in neurological as well as respiratory symptoms. However, the infected cell types responsible for acute and long-term anosmia, and the route(s) by which the virus penetrates the brain, have not been definitively identified, due to the lack of genetically manipulable mouse models that display severe disease. To address these questions, we generated conditional *hACE2*^{fl} knock-in mice that express *hACE2* in similar cell types to human and allow us to achieve cell type-specific deletion of *hACE2*^{fl} when crossed with Cre lines. *hACE2*^{fl} mice nasally inoculated with a high dose (10^5 PFU) of wild-type SARS-CoV-2 display initial infection of the olfactory epithelium and rapidly develop anosmia. This is followed by infection of neurons in the olfactory bulb and brain, which is associated with lethality and requires neuronal hACE2 expression. Whole-brain clearing and

immunofluorescence staining revealed robust SARS-CoV-2 antigen signals in the brains from high-dose infected mice, supporting efficient neuroinvasion. Although mice with neuronal-specific deletion of *hACE2*^{fl} (*BAF53b-Cre hACE2*^{fl}) survived even under high-dose infection, they still displayed viral infection in the OE and acute anosmia comparable to control mice, indicating that neuronal infection is not required for early olfactory dysfunction and that disruption of non-neuronal OE cell types is the primary cause of acute anosmia. Different with high dose infection, low-dose SARS-CoV-2 infection (10^2 PFU) was non-lethal, and a subset of *hACE2*^{fl} animals developed long-term anosmia up to 91 days. Further analysis of the tissues from these animals revealed disruption of olfactory epithelium ciliary architecture, and loss of olfactory sensory neurons, alongside persistent systemic and tissue-level immune alterations such as T cell activation/exhaustion phenotypes. Although the virus was undetectable in brain or OE tissue after long-term infection, low-level viral persistence was observed in peripheral tissues such as the lung. Our studies provide definitive genetic evidence for the cellular mechanisms of short- and long-term loss of smell and identify the pathways for brain infection during COVID-19. These studies are expected to complement existing descriptive human studies to identify causal pathogenic mechanisms and preventative and therapeutic targets.

Disclosures: M. Xu: None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.06/X22

Topic: G.04. Neuroimmunology and Neurovirology

Support: 1R01NS135072
1RF1NS138437
#409051/2022-5

Title: Blood-brain barrier dysfunction contributes to neuroinflammation and cognitive impairment in COVID-19/Long COVID mouse models

Authors: *S. E. LUTZ;
Univ. of Illinois Chicago Col. of Med., Chicago, IL

Abstract: Blood-brain barrier (BBB) permeability can cause neuroinflammation and cognitive impairment. Caveolin-1 (Cav-1) critically regulates BBB permeability, but its influence on the BBB and consequent neurological outcomes in respiratory viral infections is unknown. We used Cav-1-deficient mice with genetically encoded fluorescent endothelial tight junctions to determine how Cav-1 influences BBB permeability, neuroinflammation, and learning/memory after respiratory infection with mouse adapted (MA10) SARS-CoV-2 as a model for COVID-19 and Long COVID. We found that SARS-CoV-2 infection compromised BBB function by structural changes to tight junctions and to Caveolin-1-enriched endocytic compartments;

concordantly, we observed increased paracellular and transcellular permeability to intravenously injected fluorescent tracer molecules. This BBB leakage contributed to fibrinogen andCD4+ T lymphocyte infiltration into the hippocampus, a region important for learning and memory. Concordantly, we observed learning and memory deficits in SARS-CoV-2 infected mice. Importantly, genetic deficiency in Cav-1 attenuated transcellular and paracellular BBB disruptions, supporting that Cav-1 directly contributes to tight junction endocytosis/degradation. Moreover, genetic deficiency in Cav-1 attenuated T lymphocyte infiltration, and learning and memory deficits caused by SARS-CoV-2 infection. These results establish the contribution of Cav-1 to BBB permeability and behavioral dysfunction induced by SARS-CoV-2 neuroinflammation.

Disclosures: S.E. Lutz: None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.07/X23

Topic: G.04. Neuroimmunology and Neurovirology

Support: NIH Grant R01DA054921
NIH Grant P30DA013429
NIH Grant T32DA007237
NIH Grant T34GM136494

Title: Chronic cocaine negatively impacts Long-COVID -like outcomes produced by the SARS-CoV-2 spike protein in a rat model

Authors: *S. E. DAVIS, D. STERN, S. INAN, E. VU, D. LOPEZ, F. ANWURI, M. G. GHILOTTI, J. MEISSLER, E. M. UNTERWALD;
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Abstract: An estimated 44-48 million Americans suffer from Long-COVID following SARS-CoV-2 infection. In a report of over 100,000 people with a substance use disorder (SUD) and Long-COVID, only 4.7% were vaccinated against SARS-CoV-2. Importantly, people with SUDs have worse acute COVID-19 outcomes (severity/mortality) following SARS-CoV-2 infection than those without an SUD. Based on the low vaccination rate and worsened acute-COVID-19 outcomes associated with SUDs, we *hypothesized* that cocaine will negatively impact Long-COVID outcomes. To test our hypothesis, saline or cocaine was administered daily (*i.p.,* 15 mg/kg x 3) for 7 days to adult male Sprague Dawley rats, followed 24 hours later by an injection of either saline or the SARS-CoV-2 spike protein (*i.v.,* 500 ng/kg). Rats continued to receive saline or cocaine using a “3 days on, 4 days off” regimen wherein rats received saline or cocaine on the “on days” *(i.p.,* 15 mg/kg x 3) for 8 weeks, resulting in 4 treatment groups: control+saline, spike+saline, control+cocaine, spike+cocaine. Two months after spike administration, Long-

COVID-like outcomes were measured, including mechanical allodynia, olfaction, and anxiety-like behaviors. First, results demonstrated that spike+cocaine exposure produced a persistent reduction in weight gain compared to control-saline treatment. Second, spike+cocaine, but not spike or cocaine alone, decreased paw withdrawal thresholds in a Von Frey Test compared to controls or to baseline measurement (prior to exposure), suggesting increased pain sensitivity in these animals. Further, hippocampal levels of IL-10 positively correlated with paw withdrawal scores, a finding which agrees with previous work showing IL-10 is associated with mechanical allodynia. Third, the time spent sniffing an odor attractant was lower in rats injected with spike. Lastly, spike or cocaine significantly reduced the latency to enter the open arms of the elevated plus maze, suggesting an impulsive-like phenotype. In summary, chronic cocaine administration negatively impacted spike-induced Long-COVID-like outcomes in this rat model. These results highlight the need for clinical observations of people with co-occurring cocaine use and Long-COVID, as well as further preclinical research to understand the neurobiological mechanisms underlying these conditions.

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Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.08/X24

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AG082539
NIH Grant DA059310

Title: NLRP3 inflammasome-related microglial pyroptosis in EcoHIV infected mice

Authors: *H. LI[1], C. F. MACTUTUS[2], D. ALTOMARE[1], A. SIKIRZHYTSKAYA[1], N. VANDEGRIFT[1], M. SHTUTMAN[3], R. M. BOOZE[4];
[2]Psychology, [3]Drug Discovery and Biomed. Sci., [1]Univ. of South Carolina, Columbia, SC; [4]Dept Psychol, Univ. South Carolina, Columbia, SC

Abstract: HIV-associated neurocognitive disorders (HAND) remain a major complication in the aging HIV-1-seropositive population and are associated with persistent neuroinflammation. However, the relationship between HIV infection, microglial pyroptosis, and NLRP3 inflammasome activation remains poorly understood. In this study, C57BL/6J mice were retro-orbitally inoculated with EcoHIV and examined at 14, 30, and 60 days post-infection. Whole-brain imaging using a novel light-sheet microscopy platform (SLICE) was employed to visualize the temporal distribution of EcoHIV and the spatial association of NLRP3 inflammasome activation throughout the brain. In parallel, BV2 microglial cells were infected with EcoHIV in vitro and treated with the selective NLRP3 inhibitor (MCC950). Expression of gasdermin D

(GSDMD), NLRP3, caspase-1, HLA-DR, PD-1, and Ki67 were evaluated by immunofluorescence staining. EcoHIV-infected mice exhibited a marked increase in NLRP3 expression that peaked at 14 days post-infection and declined modestly thereafter, whereas GSDMD expression progressively increased over time. These findings reveal dynamic temporal changes in microglial pyroptosis and NLRP3 inflammasome activity during NeuroHIV progression. In vitro, EcoHIV-infected BV2 cells displayed robust eGFP fluorescence (an inserted maker of EcoHIV). EcoHIV infection significantly elevated the expression of GSDMD and NLRP3, consistent with enhanced pyroptosis. Notably, MCC950 treatment attenuated the expression of GSDMD, NLRP3, HLA-DR, PD-1, and Ki67, indicating suppresses on pyroptosis, microglial activation, and proliferative responses. Collectively, these findings identify NLRP3 inflammasome-mediated pyroptosis as a key mechanism underlying microglial dysfunction during EcoHIV infection and suggest that targeting NLRP3 signaling may represent a promising therapeutic strategy for mitigating neuroinflammation and the progression of HAND.

Disclosures: H. Li: None. **C.F. Mactutus:** None. **D. Altomare:** None. **A. Sikirzhytskaya:** None. **N. Vandegrift:** None. **M. Shtutman:** None. **R.M. Booze:** None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.09/X25

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant DA056288
NIH Grant GM130456

Title: EcoHIV-infected microglial harbor unique transcriptomic states: Implications for abnormal microglia proliferation

Authors: *K. A. MCLAURIN, B. J. VEENSTRA, T. ELDER, J. R. TURNER;
Pharmaceut. Sci., Univ. of Kentucky, Lexington, KY

Abstract: HIV-1-associated neurocognitive disorders (HAND), which afflict 50% of HIV-1 seropositive individuals, remain one of the biggest clinical challenges facing this population. The pathogenesis of HAND is driven, at least in part, by the persistent microglial viral reservoir. Historically, HIV-infected microglia have been dualistically categorized as predominantly exhibiting a pro-inflammatory, or M1, phenotype. Recent studies, however, favor investigating microglial function and transcriptional signatures across a continuum. Here, we demonstrate that chimeric HIV (EcoHIV) exacerbates microglia proliferation and sex-dependently alters the mRNA expression of key microglial ligands *in vitro*. Mixed glia were isolated from the cortex of male and female neonatal (PD 1-3) Fischer F344/NCrl rat pups. Upon reaching confluency, primary microglia were purified, treated with EcoHIV, and collected for molecular analyses (Quantitative Polymerase Chain Reaction (qPCR; *n*=5-9), *In Situ* Hybridization (*n*=3-4)). High

concordance was seen between qPCR and *in situ* hybridization. First, treatment with EcoHIV exacerbates microglia proliferation, indexed using *Pcna* (Proliferating Cell Nuclear Antigen Protein) and *Mki67* (Marker of Proliferation Ki-67), in a gene- and sex-dependent manner. Specifically, the transcriptomic expression of both *Pcna* and *Mki67* was significantly increased in EcoHIV-treated microglia isolated from male rodents. *Mki67*, but not *Pcna*, mRNA expression was significantly upregulated in EcoHIV-treated microglia purified from female rat pups. Second, with regards to microglial structure, EcoHIV-treated microglia isolated from male rodents exhibited a highly selective decrease in *Trem2* (Triggering Receptor Expressed on Myeloid Cells 2) mRNA expression relative to control treated cells. In contrast, EcoHIV-treated microglia isolated from female neonatal pups exhibited a unique response profile characterized by a statistically significant upregulation in *Csf1r* (Colony Stimulating Factor 1 Receptor) and *Dap12* (TYRO Protein Tyrosine Kinase-Binding Protein) mRNA expression, as well as a significant downregulation of *Trem2* mRNA expression. Finally, EcoHIV-induced structural alterations adversely impact downstream signaling. Indeed, independent of biological sex, EcoHIV-treated microglia displayed a robust decrease in *Ctnnb1* (Catenin Beta 1) expression coupled with a significant increase in *Syk* (Spleen Tyrosine Kinase) expression. Enhancing our understanding of how HIV-1 alters the transcriptomic signature of microglia may afford novel targets for the development of therapeutics. Funding: DA056288, GM130456.

Disclosures: K.A. McLaurin: None. **B.J. Veenstra:** None. **T. Elder:** None. **J.R. Turner:** None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.10/X26

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01 DA063181
NIH R01 DA052209
NIH R01 NS148274
UCR CIRM RAMP Program

Title: Methamphetamine modulates neurotoxicity of HIV-infected iPSC-derived microglia separately from viral production

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Abstract: The risk of developing neurocognitive impairment (NCI) is increased in people with HIV-1 infection (PWH) and methamphetamine (METH) use disorder (MUD) compared to PWH without MUD and uninfected individuals. However, the mechanisms conferring the combined

effects of METH and HIV-1 are incompletely understood. In the present study, we assessed viral production and neurotoxicity of human microglia derived from induced pluripotent stem cells (iPSC) of four different donors. Microglia were infected with HIV-1 at multiplicities of infection (MOI) ranging from 0.001 to 0.1 and in the presence and absence of METH (10 μM). Conditioned media (CM) was collected every 3 days and concentrations of HIVp24 were measured by ELISA. CM collected at the peak of viral production, if it occurred before day 12, or collected at day 12 of infection was tested for neurotoxicity using mixed cultures of iPSC-derived neurons and astrocytes at 50% final concentration. After 24 hours the neuroglial cell were fixed and neurons and nuclear DNA were fluorescence labeled. Analysis by quantitative microscopy showed that HIV and METH both caused loss of neurons with the combination of HIV and METH often resulting in the most pronounced toxicity. However, different HIV MOIs varied in their effect in that the highest MOI did not always produce the highest level of neurotoxicity. Therefore, while METH can increase HIV neurotoxicity, the extent of neuronal injury (and NCI) may depend on the HIV inoculum and the intensity of the host's response in the brain.

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Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.11/X27

Topic: G.04. Neuroimmunology and Neurovirology

Support: NINDS 5R01AI1725-02

Title: Understanding Post Treatment Lyme Disease Syndrome: Examining the effect of patient serum antibodies on behavior in mice

Authors: *A. LEE[1,2], K. MYKYTEN[2], Y. ZHONG[3], S. NG[4], A. MARQUES[4], P. GWYNNE[3], L. HU[3], C. G. DULLA[2];
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Abstract: 10-20% of patients treated for Lyme disease (LD) develop persistent symptoms of fatigue, musculoskeletal pain, and/or cognitive dysfunction in a condition termed post-treatment Lyme disease syndrome (PTLDS). The cause of PTLDS is unknown but key to developing diagnostic and therapeutic tools. PTLDS is hypothesized to arise from autoantibody generation in the acute phase of LD. A few studies have investigated the link between autoantibodies and PTLDS in humans, but none have been studied in animal models. Here, we present a mouse model to study antibody-mediated immune dysregulation in PTLDS.
To test possible autoimmune effects of PTLDS we isolated immunoglobulin (IgG) from serum collected from patients with PTLDS and controls, and injected them into 8-10-week-old female

C57 mice. IgG was isolated from serum collected from: 1) controls from geographical regions where LD is not prevalent and who have not been exposed to LD (n=10), 2) patients previously infected with LD, but without symptoms of PTLDS (n=12), and 3) patients previously infected with LD and who went on to develop symptoms of PTLDS (n=16). Behavioral experiments were performed blind to the serum condition. Two injection paradigms were examined to test the behavioral response to IgG injection: 1) a single dose or 2) 4 repeated doses over 4 days. Both paradigms started with a pre-injection baseline behavioral measurement. In the single injection paradigm, the mice underwent behavioral testing daily for 3 days post-injection. In the repeated injection paradigm, the mice underwent behavioral testing for 4 days post-injection, with 1 injection per day. Behavioral tests included Spontaneous Y-Maze Alternation, Grip Strength, the Cold Plantar Assay, and the Hot Water Tail Immersion Assay. These tests were chosen to investigate mouse phenotypes that might be relevant to PTLDS symptoms, including cognitive dysfunction, musculoskeletal pain, fatigue, and thermal sensitivity or numbness.
We found that a single injection did not cause a behavioral phenotype in mice. Preliminary data from mice that received 4 injections of IgG suggest they exhibit decreased locomotor output and decreased sensitivity to heat and cold stimuli, as compared to mice injected with 4 injections of IgG from patients who had LD but did not develop PTLDS. Our preliminary results suggest that 4 injections may be necessary to detect differential responses between mice in different experimental groups. Future work will include adding additional human PTLDS and control samples to our rodent behavioral test and correlating human PTLDS symptomatology with rodent behaviors resulting from injection with individual patient serum.

Disclosures: A. Lee: None. **K. Mykyten:** None. **Y. Zhong:** None. **S. Ng:** None. **A. Marques:** None. **P. Gwynne:** None. **L. Hu:** None. **C.G. Dulla:** None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.12/X28

Topic: G.04. Neuroimmunology and Neurovirology

Support: Hypothesis Fund

Title: Cholera toxin-induced sickness behaviors and brain-specific transcriptomic changes in female mice

Authors: *B. COSTA LIMA[1], A. ROGINSKI[2], J. L. VERPEUT[3], M. O. DIETRICH[5], E. BORGES FLORSHEIM[4];
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[4]Biodesign Ctr. for Hlth. Through Microbiomes, Arizona State Univ., TEMPE, AZ;
[5]Comparative Med., Yale Univ., New Haven, CT

Abstract: Diarrheal diseases remain a major global public health challenge. Cholera, one of the top 5 diarrheal diseases, is caused by a toxin-producing *Vibrio cholerae* bacterium. Cholera toxin (CTx) is responsible for 1.3-4 million cholera cases per year and is a potent mucosal adjuvant used in vaccine development, demonstrating its clinical and immunological relevance. Yet, the acute effects of CTx on behavior and the brain have received limited attention. To address this, we established a mouse model of food poisoning using CTx to evaluate toxin-induced behavioral changes and its effects on gene expression in brain tissue. Female BALB/c mice were intragastrically exposed to CTx (0.8 mg/kg) and presented diarrhea, hypothermia, gut edema and inflammation. Six (6) hours following the oral gavage, we 1) conducted behavioral analyses such as the forced swimming test (FST) to investigate the development of depressive-like behavior and quantification of kaolin intake to assess the emergence of pica behavior as a behavioral proxy for nausea; 2) collected specific brain regions (cerebellum, pons, medulla, hippocampus, hypothalamus and frontal cortex) for evaluating CTx-induced transcriptional changes using RT-qPCR. Group differences were calculated using student *t* or Mann-Whitney tests. CTx-treated female mice developed depressive-like behavior, indicated by an increased time spent in immobility and a decreased distance traveled in the FST, and did not develop pica behavior (nausea) when compared to vehicle-treated controls. In the brain, we found that CTx significantly upregulated *Il33*, *neuroserpin*, *Tnfa* and *Tjp1* and downregulated the *Ccl1* gene expressions in the cerebellum and upregulated the expression of *Sod1* in the hypothalamus (all relative to *Rpl13a*). No significant changes were found in other evaluated genes and regions. These findings suggest that intragastric CTx induces sickness behaviors similar to those observed in infectious states, indicating that non-infectious inflammatory stimuli can also affect the brain and alter behavior. Our qPCR data suggests that CTx exposure triggers region-specific acute neuroinflammation and oxidative stress, while inducing a neuroprotective response in the brain. Currently, we are leveraging iDisco+ and light-sheet microscopy to monitor brain-wide neural activity changes following CTx ingestion. We are also investigating the specific neuroimmune mechanisms driving CTx-induced depressive-like behavioral responses. These results advance the understanding of how gastrointestinal toxins affect the brain and behavior and inform future therapeutic interventions for inflammation-related diseases.

Disclosures: B. Costa Lima: None. **A. Roginski:** None. **J.L. Verpeut:** None. **M.O. Dietrich:** None. **E. Borges Florsheim:** None.

Poster

PSTR355: Viral and Infectious Mechanisms of Neuroinflammation II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.14/X29

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: RLS Foundation

Title: Cortisol-Induced Microglial miR-124-3p as a Potential Mediator of Brain Iron Deficiency in Restless Legs Syndrome

Authors: *K. PALSA[1], A. SAHU[2], D. B. RYE[3], J. R. CONNOR[2];
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Abstract: Restless Legs Syndrome (RLS) affects approximately 5-10% of the population and is associated with brain iron deficiency, a process regulated by blood-brain barrier endothelial cells (BBBECs). Our previous studies demonstrated that miR-124-3p is elevated in cerebrospinal fluid (CSF)-derived extracellular vesicles from patients with RLS and directly targets the 3′ iron-responsive element (IRE) of transferrin receptor 1 (TfR1) mRNA, resulting in reduced TfR1 expression and impaired iron uptake. However, the mechanisms underlying the increased expression of miR-124-3p in RLS remain unclear. Because cortisol has been shown to induce miR-124-3p expression and elevated cortisol levels have been reported in RLS, we investigated the relationship between cortisol and iron dysregulation using CSF samples from patients with RLS and controls, as well as postmortem brain tissues and C57BL/6 mice. We found that CSF from patients with RLS contained significantly higher cortisol levels and lower estradiol levels compared with controls. Although no significant differences were observed in IL-6 or neurofilament light chain (NfL) levels, increased Iba1 expression indicated enhanced microglial activation, which was associated with elevated miR-124-3p expression in the RLS group. Furthermore, corticosterone administration in mice reduced TfR1 and H-ferritin expression in brain microvasculature, consistent with increased miR-124-3p expression and impaired iron transport and storage. Collectively, these findings suggest that elevated cortisol promotes microglial activation and upregulation of miR-124-3p, leading to decreased TfR1 expression, reduced iron uptake across the blood-brain barrier, and subsequent brain iron deficiency in RLS. These results identify a potential cortisol-microglia-miR-124-3p pathway that contributes to the pathophysiology of RLS and may represent a novel therapeutic target for restoring brain iron homeostasis.

Disclosures: K. Palsa: None. **A. Sahu:** None. **D.B. Rye:** None. **J.R. Connor:** None.

Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.01/X30

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NINDS R35NS122336
NIDILRR 90SIMS0015
NIDILRR 90SIMS0011

Title: Spasticity as a Biomarker of Motor Recovery Following Severe Spinal Cord Injury

Authors: D. DE SANTIS[1,3], B. CHEN[3,2], ***M. A. PEREZ**[2,3];
[1]Arms and Hands lab, [2]Shirley Ryan Abilitylab, Chicago, IL; [3]Hines VA Hosp., Hines, IL

Abstract: Severe motor complete spinal cord injury (SCI) is associated with limited neurological recovery; however, a subset of individuals regains motor function below the lesion level. Current prognostic biomarkers, including neurological examination and MRI, have limited ability to identify individuals with recovery potential early after injury. Emerging evidence suggests that spasticity may reflect preserved descending connectivity and could serve as a biomarker of recovery. We conducted a prospective multicenter observational study to determine whether spasticity predicts neurological recovery during inpatient rehabilitation. A total of 114 individuals with motor complete cervical or thoracic SCI (AIS A/B) were enrolled across three U.S. Spinal Cord Injury Model System centers between 2021 and 2025. Neurological examinations and spasticity assessments were performed at admission (26±22 days post-injury) and discharge (67±29 days post-injury). The primary outcome was presence of lower extremity motor recovery, defined as an increase in lower extremity motor score (LEMS). Spasticity was quantified using the pendulum test first swing angle (FSA), with values <96.7° indicating spasticity. Individuals who showed a positive change in LEMS scores at discharge increased an average of 10±9 points. Notably, we found that all individuals who demonstrated lower extremity motor recovery at discharge exhibited spasticity. Logistic regression identified FSA ($p=0.019$) and lower extremity sensory sparing ($p=0.005$) as independent predictors of presence of motor recovery ($\chi^2=20.0$, $p<0.001$, Nagelkerke $R^2=0.273$). In individuals without sensory sparing, the presence of spasticity increased the predicted probability of motor recovery from 5% to 21%. Residual sensory function further increased recovery probability by approximately 10% for every 10-point increase in sensory scores. These findings identify spasticity as a clinically accessible prognostic marker of motor recovery after motor complete SCI and support its incorporation into routine inpatient neurological assessments.

Disclosures: D. De Santis: None. **B. Chen:** None. **M.A. Perez:** None.

Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.02/X31

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: New Jersey NJCSCR #CSCR25ERG003

Title: Using muscle functional MRI to quantify spatial patterns of quadriceps activation in able-bodied participants and individuals with spinal cord injury

Authors: *P. BARRANCE[1,4], G. H. YUE[1,4], B. YAO[2,4], G. R. WYLIE[2,4], G. F. FORREST[3,4]; [1]Ctr. for Mobility and Rehabil. Engin. Res., [2]Rocco Ortenzio Neuroimaging Ctr., [3]Tim and Caroline Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ; [4]Dept. of Physical Med. and Rehabil., Rutgers New Jersey Med. Sch., Newark, NJ

Abstract: Quantifying how muscle activation is spatially distributed across muscles remains a challenge in studies of neuromuscular recovery following spinal cord injury (SCI). Existing approaches, primarily electromyography (EMG), provide localized sampling or predominantly temporal information, limiting their ability to capture the spatial organization of muscle activation. Muscle functional MRI (mfMRI) offers an approach for mapping activation across entire muscles by measuring exercise-induced changes in the transverse relaxation time (T2) of muscle water, which reflects underlying metabolic activity. In this study, we apply mfMRI to characterize spatial patterns of quadriceps activation during a controlled knee extension task. Participants complete a supine quadriceps exercise protocol with resistance provided by ankle weights. Baseline and post-exercise scans are acquired to calculate T2 shifts (ΔT2). Muscles are segmented across multiple image slices, and activation patterns are constructed by combining ΔT2 values across muscles and slice locations. Exercise-related increases in T2 are consistently observed across muscles and slices in able bodied participants, supporting the feasibility of this approach for quantifying distributed muscle activation. Participants with SCI are being enrolled for imaging using the same acquisition and analysis framework, enabling comparisons of activation magnitude and spatial distribution with able-bodied controls. We hypothesize that individuals with SCI will demonstrate reduced T2 shifts and altered spatial activation patterns compared with controls. This work aims to establish mfMRI as a tool for quantifying spatial muscle activation and to provide insight into neuromuscular adaptation following SCI.

Disclosures: P. Barrance: None. **G.H. Yue:** None. **B. Yao:** None. **G.R. Wylie:** None. **G.F. Forrest:** None.

Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.03/X32

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH T32 HD101395

Title: Increased motor unit excitability and the presence of ankle clonus following spinal cord injury

Authors: *A. BENEDETTO[1,3], M. FARLEY[4], E. CURUK[3], B. CHEN[5], J. A. BEAUCHAMP[6], C. HECKMAN[2], M. A. PEREZ[7], G. E. PEARCEY[8];
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Abstract: Ankle clonus is a common involuntary motor behavior following Spinal Cord Injury (SCI), characterized by rhythmic muscle contractions and joint oscillations. It has been primarily attributed to increased spinal reflex excitability and reduced descending inhibition after SCI, but the exact mechanisms are not well understood. It has been suggested, but not confirmed in humans, that the recovery of motoneuron persistent inward currents (PICs) may contribute to the development of clonus. To explore this, we collected high density surface electromyograms from the tibialis anterior (TA) and soleus (SOL) muscles in participants with SCI (8 with clonus, 8 without clonus) and 13 non- injured (NI) participants, and we then characterized their motor unit behaviors. Each participant performed triangular submaximal isometric dorsiflexion and plantarflexion contractions to a peak of 30% of their maximum voluntary contraction using EMG feedback, and blind source separation algorithms were used to identify motor unit (MU) spike times. Altogether, 4,587 MUs were analyzed (SCI SOL = 1,072; SCI TA = 1,122; NI SOL = 1,474; NI TA = 1,122). The number of MUs varied across participants, and the per trial average was higher in the NI group for SOL (35.1 ± 16.0 vs. 25.9 ± 7.9; $p = 0.01$, $d = 1.1$), but there was no group difference for TA (SCI TA = 26.7 ± 6.6 vs. NI TA: 21.9 ± 9.1, $p = 0.1$). Overall group analysis revealed maximum firing rates (pps) were significantly reduced in the SCI participants compared to the NI group for both the TA (13.1 vs. 17.3, $p < 0.001$, $d = 1.8$) and the SOL (8.9 vs. 10.6, $p = 0.02$, $d = 0.72$). Subgroup analysis revealed the SCI clonus participants had lower firing rates than the SCI no-clonus participants on average across muscles (9.7 vs. 13.1, $p = 0.03$, $d = 1.7$). PIC amplitudes were estimated by quantifying firing rate hysteresis using the paired-MU analysis technique (ΔF). There were no group differences in the raw values, but there was a significant increase in the SCI group for both muscles when normalized to descending rate modulation (SCI = 0.41, NI = 0.32; $p = 0.02$, $d = 0.42$). There were no subgroup differences between the SCI participants with and without ankle clonus (Clonus = 0.37, No-Clonus = 0.44; $p = 0.5$). Although we did not observe significant differences in between clonus subgroups within the SCI group, a sub-analysis revealed a significant correlation of ΔF with the H-reflex in the SOL ($r = 0.6$, $p = 0.04$) and a possible relationship to clonus that warrants further investigation. Additional analyses are being performed that will be presented in person, and new participants are being actively recruited .

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Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.04/Y1

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Grant R35NS122336

Title: Motor Unit Loss and Neuromuscular Transmission Deficits in Lower Extremity Muscles following Chronic Cervical and Thoracic Spinal Cord Injury

Authors: *M. T. FARLEY[1], M. A. PEREZ[1,2,4,3];
[1]Ctr. for Neural plasticity, Arms & Hands, Shirley Ryan AbilityLab, Chicago, IL; [2]Dept. of Physical Med. and Rehabil., [3]Dept. of Physical Therapy and Human Movement Sci., Northwestern Univ., Chicago, IL; [4]Edward Jr. Hines VA Hosp., Hines, IL

Abstract: Electrophysiological evidence suggests that spinal cord injury (SCI) can induce changes in the peripheral motor system below the level of injury, including muscle fiber denervation and motor unit loss. However, the extent of motor unit loss and neuromuscular transmission impairment following SCI remains poorly understood. In this study, we used motor unit number estimation (MUNE) derived from compound muscle action potential (CMAP) scans and low-frequency (3 Hz) repetitive nerve stimulation (LF-RNS) to assess motor unit function and neuromuscular transmission, respectively, in the tibialis anterior (TA) and abductor hallucis (AH) muscles of individuals with chronic cervical and thoracic SCI and healthy controls. Compared to controls, participants with SCI exhibited lower MUNE values in both the TA and AH muscles. LF-RNS revealed impaired neuromuscular transmission, with >10% decrements in CMAP area between the first and fifth responses in both TA and AH muscles in the SCI group. Control participants had <10% CMAP area decrement during LF-RNS. These findings suggest that chronic SCI is associated with both motor unit loss and impaired neuromuscular transmission in muscles innervated by motoneurons located several segments below the injury level, and highlight the need to consider peripheral motor system dysfunction when developing and optimizing rehabilitation strategies aimed at restoring motor function.

Disclosures: M.T. Farley: None. **M.A. Perez:** None.

Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.05/Y2

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH/NINDS R35 NS122336

Title: Measurements of Knee Torque in Individuals with and without Spinal Cord Injury

Authors: *M. LEE[1], D. DE SANTIS[4], M. FARLEY[2], M. PRIOVOLOS[3], J. FERNANDEZ[3], M. A. PEREZ[5];
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Abstract: Recovery of knee extensor function is a major determinant of walking ability after spinal cord injury (SCI). Accurate and quantitative assessment of knee torque is therefore essential for monitoring recovery and evaluating therapeutic interventions. Although isokinetic dynamometers are considered the gold standard for torque measurement, their cost, size, and

limited portability restrict their use in routine clinical practice. We developed a portable instrumented knee brace equipped with bilateral torque sensors capable of measuring isometric knee flexion and extension torque. The purpose of this study is to evaluate the validity, feasibility, and reliability of this wearable device in individuals with and without SCI. Adults with SCI and neurologically intact controls will perform maximal voluntary isometric knee flexion and extension contractions while seated. Torque measurements obtained using the instrumented brace will be compared with measurements obtained using a Biodex Rehabilitation System 4 dynamometer. To assess clinical feasibility, additional measurements will be obtained in a supine position using the instrumented brace. Surface electromyography (EMG) will be recorded from quadriceps and hamstring muscles during contractions. Clinical assessments, including the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) examination and Modified Ashworth Scale, will be collected to characterize motor impairment and spasticity. Participants will complete repeated testing sessions to assess test-retest reliability. We hypothesize that torque measurements obtained from the instrumented knee brace will demonstrate strong agreement with Biodex measurements and provide reliable quantitative assessments across testing sessions. Furthermore, we expect the brace to enable objective strength measurements in positions that are difficult to assess using conventional dynamometry. These findings may support the development of accessible and portable technologies for quantitative motor assessment in individuals with SCI and facilitate longitudinal monitoring in both clinical and community settings.

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Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.06/Y3

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Tim Reynolds Foundation

Title: Machine Learning based continuous Blood Pressure estimation for monitoring and closed-loop stabilization after Spinal Cord Injury

Authors: *M. RAVI, A. BHEEMREDDY, M. B. BAYRAM, G. F. FORREST;
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Abstract: Blood pressure instability is a common and clinically important consequence of spinal cord injury (SCI), contributing to orthostatic symptoms, reduced activity tolerance, and poorer quality of life. Continuous blood pressure monitoring could improve the detection and management of these hemodynamic disturbances, but intermittent cuff-based measurements are often not sufficient to capture rapid or posture-related changes in blood pressure in this

population. Prior work in SCI also suggests that continuous blood pressure sensing may be an important step toward closed-loop strategies for blood pressure stabilization using spinal cord stimulation.This study explores a personalized approach for estimating blood pressure from photoplethysmography (PPG) and electrocardiography (ECG) using machine learning. Rather than replacing cuff measurements entirely, the approach uses periodic cuff-based readings to personalize blood pressure estimates for each participant, with the goal of reducing the need for frequent recalibration over time. This personalized framework is intended to support more continuous and practical blood pressure tracking while remaining anchored to clinically familiar measurements. The modeling approach is informed by PulseDB, a large physiological waveform dataset developed for benchmarking blood pressure estimation methods from ECG and PPG signals. Both PPG-only and combined PPG+ECG approaches are being considered to identify practical strategies for individualized blood pressure estimation in SCI. The broader goal is to establish a foundation for continuous blood pressure measurement with minimal calibration burden, as a crucial step toward future wearable monitoring solutions and stimulation-based systems for continuous blood pressure stabilization after SCI.

Disclosures: M. Ravi: None. **A. Bheemreddy:** None. **M.B. Bayram:** None. **G.F. Forrest:** None.

Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.07/Y4

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NKRDPC Grant 2024YFA1108200

Title: Neural stem cells derived from human fetal brain for spinal cord injury: A dose-escalation phase 1trial

Authors: *L. CHENG, Z. WU;
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Abstract: Spinal cord injury (SCI) has limited restorative treatment options, and the clinical translation of neural stem cell therapy remains constrained by small early-phase datasets. We conducted a single-center phase Ia 3+3 dose-escalation trial (ChiCTR2200059595) to evaluate intrathecal transplantation of GMP-grade human neural stem cells (hNSCs) for thoracic or lumbar SCI. Preclinical studies showed that hNSCs have low immunogenicity and high neuronal differentiation ability. Eligible participants were aged 18-60 years, had AIS grade A-D injury in the non-acute period (2 weeks to 12 months after injury), and received a single intrathecal injection without immunosuppressants across four planned dose cohorts (1.5 million, 5.0 million, 15 million or 50 million; n=3 per cohort). Twelve participants completed follow-up. Safety

endpoints included adverse events (AEs), treatment-related AEs (TRAE), serious AEs (SAEs) and dose-limiting toxicity (DLT); exploratory outcomes included ASIA motor/sensory scores, neurological level of injury (NLI), Functional Independence Measure (FIM), Walking Index for SCI (WISCI), Spinal Cord Independence Measure (SCIM-III), and serial CSF proteomics before treatment, at day 7 and at 6 months. Forty-nine AEs were recorded, including 14 TRAEs; all were mild clinical symptoms or laboratory abnormalities. No SAE or DLT occurred. Transient tumor-marker elevations in one participant were not associated with tumor formation on PET-CT. Lower-limb motor scores improved in 7/12 participants (58.3%), with 3/12 (25%) reaching the SCI minimal clinically important difference (MCID, ≥ 4-point motor score improvement). Sensory scores improved in 6/12 participants (50%), and one participant showed a one-dermatome improvement in NLI. FIM motor scores and SCIM-III scores improved or remained unchanged (for participants with full baseline scores) in all participants, and WISCI scores improved in 6/12 (50%). CSF proteomics identified time-dependent changes enriched in pathways related to neurodevelopment, axonogenesis, extracellular matrix remodeling, angiogenesis and growth-factor signaling. Inflammatory proteins showed minimal fold changes, with no evidence of therapy-induced inflammation. These phase Ia data demonstrate the feasibility and safety of intrathecal hNSCs transplantation for patients with thoracic and lumbar SCI.

Disclosures: L. Cheng: None. **Z. Wu:** None.

Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.08/Y5

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: EU H2020 program, Grant nr. 681094—NISCI)
Wings for Life
Swiss Paraplegic Foundation
Wyss Zurich
Swiss Federal Ministery of Education and Research
NovaGo Therapeutics AG

Title: Anti-Nogo-A Antibodies enhance functional Recovery after Spinal Cord Injury in Humans; the Clinical Trials NISCI and SPROUT-1

Authors: *M. E. SCHWAB[1,3], S. MOESE[3], B. ZÖRNER[4], N. WEIDNER[5], A. CURT[2]; [1]Univ. of Zurich, Schlieren, Switzerland; [2]Univ. of Zurich, Zurich, Switzerland; [3]Novago Therapeut. AG, Schlieren, Switzerland; [4]Swiss Paraplegic Ctr., Nottwil, Switzerland; [5]Heidelberg Univ. Hosp., Heidelberg, Germany

Abstract: Antibodies against the oligodendrocyte and neuronal membrane protein Nogo-A enhance regenerative and compensatory neurite growth in animal models of different types of CNS injuries including spinal cord injury, along with higher levels of functional recovery. A recent Phase 2 clinical study with the anti-Nogo-A antibody NG101/ATI355 in acute spinal cord injury patients with cervical injuries (NISCI trial; NCT03935321; randomized, controlled trial with verum : placebo 2:1, 130 patients) has shown significantly improved upper extremity motor scores and SCIM-3 independence/quality of life scores in the patients with incomplete injuries (Weidner et al., 2025; Scheuren et al., 2026; Farner et al., 2026). As NG101 is not available anymore for technical reasons, a new, optimized, high affinity, highly stable, fully human monoclonal anti-Nogo-A antibody, NG004, has been developed. Toxicology and pharmacokinetics of intrathecal NG004 were studied in Cynomolgus monkeys (Kunz et al., 2025). A dose escalation and safety trial, SPROUT-1 (NCT06817577), was conducted in acute, motor incomplete tetraplegic patients. Results show excellent safety of NG004 if injected intrathecally as 6 injections over 30 days (5+/-2 days intervals between injections; first injection within 4-28 d. after injury). While the number of patients was limited and did not allow statistical analysis, the majority of the patients reached levels of their upper extremity motor scores well above the mean of the placebo group of the previous NISCI trial. A placebo controlled, double blind proof-of-concept trial with NG004 in 120 patients is currently in progress at 14 clinical sites of the European EMSCI clinical network. *NISCI and SPROUT clinical teams: Swiss Paraplegic Center, Nottwil, Switzerland; University Hospital Balgrist, Zurich, Switzerland; REHAB Basel, Basel, Switzerland; Center for Paraplegiology, University of Heidelberg, Germany; BG Accident Clinic Murnau, Germany; Clinic for Paraplegia, Clinic Hohe Warte Bayreuth, Germany; BG Clinic Bergmannstrost Halle, Germany; Orthopedic Clinic Hessisch-Lichtenau, Germany; Center for Spinal Cord Injury, Trauma Center, Berlin, Germany; BG University Hospital Bergmannsheil, Bochum, Germany; BG Clinic Tübingen, Germany; Fundacio Institute Guttmann, Badalona, Spain; Dept. of Rehabilitation and Sports Medicine, University Hospital Motol, Prague, Czech Republic*

Disclosures: M.E. Schwab: A. Employment/Salary (full or part-time):; NovaGo Therapeutics. 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.; NovaGo Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NovaGo Therapeutics. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); none. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NovaGo Therapeutics. F. Consulting Fees (e.g., advisory boards); none. Other; none. **S. Moese:** A. Employment/Salary (full or part-time):; NovaGo Therapeutics. 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.; NovaGo Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NovaGo Therapeutics. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); none. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NovaGo Therapeutics. F. Consulting Fees (e.g., advisory boards); none. Other; none. **B. Zörner:** 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.; NovaGo Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NovaGo Therapeutics. F. Consulting Fees (e.g., advisory boards); NovaGo Therapeutics. **N. Weidner:** 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.; NovaGo Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NovaGo Therapeutics. F. Consulting Fees (e.g., advisory boards); NovaGo Therapeutics. **A. Curt:** A. Employment/Salary (full or part-time):; NovaGo Therapeutics. 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.; NovaGo Therapeutics. F. Consulting Fees (e.g., advisory boards); NovaGo Therapeutics.

Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.09/Y6

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: U.S. Department of Defense (W81XWH2210478)
Brooks Rehabilitation–University of Florida College of Public Health and Health Professions Research Collaboration
Dr. Bogard is supported by a Gator NeuroScholars Fellowship funded by the Evelyn F. and William L. McKnight Brain Institute at the University of Florida in partnership with an anonymous family foundation

Title: Sleep Fragmentation Attenuates Acute Intermittent Hypoxia-Induced Respiratory Motor Plasticity After Spinal Cord Injury

Authors: *A. T. BOGARD[1,2,3,7,4], M. J. MIR[5,1,7,3], H. SNYDER[2,1,3], J. DUNN[7], J. ENCARNACION[7], R. WAZIRY[6,1], G. S. MITCHELL[2,3,1,4], E. J. FOX[1,3,2,7,4];
[2]Physical Therapy, [3]Breathing Res. and Therapeut. Ctr., [4]McKnight Brain Inst., [5]Speech, Language, and Hearing Sci., [6]Epidemiology, [1]Univ. of Florida, Gainesville, FL; [7]Brooks Rehabil., Jacksonville, FL

Abstract: Although therapeutic acute intermittent hypoxia (tAIH) elicits respiratory motor plasticity after spinal cord injury (SCI), ~40% of individuals show minimal functional improvement. Sleep apnea is highly prevalent after SCI and may contribute to tAIH response variability. Mild-to-moderate sleep apnea is linked to greater tAIH-induced motor gains, suggesting nocturnal hypoxia may precondition subsequent plasticity. However, recurrent apneas also fragment sleep, which may independently impair neuroplastic responses. Experimental evidence demonstrates that tAIH-induced plasticity depends on the balance between serotonin-

and adenosine-dependent mechanisms. Most human protocols target serotonin-dependent plasticity through brief, mild hypoxic episodes, yet sleep disruption may increase adenosine-mediated inhibition of plasticity. Since elevated CO2 enhances hypoxia-induced chemoreceptor activation, it may strengthen respiratory motor plasticity. Thus, we tested the hypothesis that sleep fragmentation reduces AIH responsiveness, whereas hypercapnic AIH (AIHH) preserves responsiveness despite sleep fragmentation. Nineteen individuals with chronic SCI (14 cervical; 16 motor complete; 10 ± 11 years post injury) completed 3 randomized 5-day intervention blocks consisting of 15 x 60s episodes of sham (21% O2), AIH (9% O2), or AIHH (9% O2 + 5% CO2), separated by 90s normoxic intervals, followed by respiratory strength training. Overnight sleep monitoring quantified nocturnal hypoxia and sleep fragmentation using composite indices derived from principal component analysis. Maximal inspiratory pressure (MIP) was assessed pre-intervention and 1-7 days post-intervention; responsiveness was defined as a ≥5% increase in MIP. Bayesian logistic regression estimated odds ratios (ORs), 95% credible intervals (CrI), and posterior probabilities. Greater sleep fragmentation was associated with a 99.5% probability of reduced responsiveness following AIH (OR = 0.31, 95% CrI [0.08, 0.79]), whereas nocturnal hypoxia showed a weaker, less certain association (OR = 0.58, 95% CrI [0.26, 1.03]). In contrast, clear associations were not observed between AIHH responsiveness and either sleep fragmentation (OR = 0.93, 95% CrI [0.41, 2.23]) or nocturnal hypoxia (OR = 0.76, 95% CrI [0.45, 1.24]). Thus, sleep fragmentation appears to attenuate AIH- but not AIHH-induced respiratory motor plasticity. Targeting sleep-related constraints on neuroplasticity may therefore enhance responsiveness to intermittent hypoxia-based neuromodulation after SCI.

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Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.10/Y7

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Wings for Life (Accelerated Translational Program)

Title: Safety and Efficacy of NVG-291 in Chronic Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2a Trial

Authors: *B. CHEN[1,2,3], J. D. GUEST[4], B. K. KWON[5], E. GRANT[6], L. JONES[7], S. KIRSHBLUM[8], D. P. LAMMERTSE[9], R. KAYE[10], M. A. DEPAUL[10], M. A. PEREZ[2,1,3]; [1]Hines VA Hosp., Hines, IL; [2]Shirley Ryan AbilityLab, Chicago, IL; [3]Dept. of Physical Med. and Rehabil., Northwestern Univ., Chicago, IL; [4]Neurolog. Surgery/Miami Project to Cure Paralysis, Univ. of Miami Miller Sch. of Med., Miami, FL; [5]Orthopaedics / ICORD, ICORD, UBC, Vancouver, BC, Canada; [6]DP Clin., Washington, DC; [7]Thomas Jefferson Univ.,

Philadelphia, PA; [8]Kessler Inst., West Orange, NJ; [9]Craig Hosp., Englewood, CO; [10]NervGen Pharma, Vancouver, BC, Canada

Abstract: Restoring function after chronic spinal cord injury (SCI) remains a significant unmet need, partly due to inhibitory extracellular matrix signaling that limits neural repair following initial spontaneous recovery. NVG-291 is a subcutaneously administered synthetic 35 amino acid peptide derived from receptor protein tyrosine phosphatase sigma, a receptor for chondroitin sulfate proteoglycans (CSPGs). By modulating inhibitory CSPG signaling, NVG-291 is designed to overcome these inhibitory pathways and promote CNS repair through regeneration, plasticity, and remyelination. We report results from a 16-week, randomized, double-blind, placebo-controlled Phase 1b/2a trial (NCT05965700) in 20 individuals with chronic cervical motor incomplete SCI. Participants received daily NVG-291 or placebo for 12 weeks alongside daily exercise, followed by a 4-week observation period with daily exercise alone. NVG-291 was well tolerated, with no treatment-related serious adverse events. At week 12, NVG-291 increased corticospinal excitability, measured by motor evoked potential amplitude in the first dorsal interosseous (FDI) muscle (+9.43% of maximal M-wave, p=0.0155), with no effect in the tibialis anterior (TA). Exploratory analyses showed reduced reticulospinal pathway contribution (FDI: -26.52% of maximal M-wave; p=0.0280; TA: -30.88% of maximal M-wave, p=0.0062) and an inverse relationship between corticospinal and reticulospinal outputs in the FDI (NVG-291 Pearson R=-0.79, p=0.006; Spearman ρ=-0.76, p=0.011), an association absent with placebo (Pearson R=0.15, p=0.673; Spearman ρ=0.02, p=0.960), consistent with a physiological effect across descending motor pathways. Functionally, NVG-291 improved hand performance (GRASSP Quantitative Prehension, NVG-291: +3.7 versus placebo: +0.4). These findings provide preliminary evidence supporting the safety and physiological effect of NVG-291.

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Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.11/Y8

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: 5R35NS122336

Title: Augmenting Functional Recovery After Spinal Cord Injury Through a Triple-Combinatorial Intervention

Authors: B. CHEN[1,2,3], M. FARLEY[2], *A. CHANG[2,1], M. A. PEREZ[2,1,3], A. KESSLER[2]; [1]Hines VA Hosp., Hines, IL; [2]Shirley Ryan AbilityLab, Chicago, IL; [3]Dept. of Physical Med. and Rehabil., Northwestern Univ., Chicago, IL

Abstract: Recovery after spinal cord injury (SCI) can be enhanced through combinatorial interventions such as Hebbian stimulation followed by exercise. The goal of our study was to investigate whether 4-aminopyridine (4-AP), a voltage-gated potassium channel blocker known to improve axonal conduction and synaptic transmission, augments Hebbian stimulation induced plasticity in humans with chronic SCI. Participants with chronic SCI were randomly assigned to receive 40 sessions of a combinatorial intervention consisting of either 4-AP or placebo paired with Hebbian stimulation and exercise. The 4-AP group received 10 mg prior to each session and an additional 10 mg 12 hours later, while the control group received matched placebo. Hebbian stimulation consisted of 720 paired stimuli designed to elicit corticospinal volleys via thoracic spinal stimulation timed to arrive 1-2 ms before antidromic activation of motoneurons through bilateral peripheral nerve stimulation (femoral, common peroneal, and posterior tibial nerves), targeting quadriceps femoris, tibialis anterior, and soleus muscles. Physiological outcomes included motor evoked potentials (MEPs) and maximal voluntary contractions (MVCs), while functional outcomes included 10-meter walk test (10MWT), 6-minute walk test (6MWT), and electrical perceptual threshold (EPT). Assessments were conducted at baseline, after 20 sessions, and after 40 sessions. We found that MEP size and maximal voluntary contractions in all muscles targeted increased after 20 sessions and further increased after 40 sessions but to a larger extent in participants that received double-dose 4-AP compared to the group that received placebo. In addition, walking speed (measured by the 10-meter walk test) and endurance (measured by the 6-minute walk test) largely enhanced after 20 sessions and further improved after 40 sessions compared with baseline in the double-dose 4-AP group. Sensory function (measured by EPT) improvement was observed in the double-dose 4-AP group. Comparison with prior data using a single pre-stimulation dose of 4-AP revealed that the additional dose administered 12 hours later further enhanced both physiological and functional outcomes. These findings demonstrate that 4-AP potentiates Hebbian stimulation-induced plasticity and functional recovery in chronic SCI. A triple-combinatorial approach integrating neuromodulation, pharmacological facilitation, and exercise may represent a promising strategy to maximize rehabilitation outcomes.

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Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

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Program #/Poster #: PSTR356.12/Y9

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Department of Veterans Affairs Rehabilitation Research Development and Translation Career Development Award-1 (1IK1RX005028-01)

Title: Testosterone as a mediator of parasympathetic autonomic function following spinal cord injury: preliminary evidence for intranasal replacement therapy

Authors: *D. C. ARNERO[1,2,3], C. N. SIGAFOSE[1,2], F. E. CASTANO[2], T. W. SUTOR[1,3], J. M. WECHT[2,3,4], N. Y. HAREL[2,5,3], J. A. GOLDSMITH[2,5,3];
[1]Bronx Veterans Med. Res. Fndn., Bronx, NY; [2]James J. Peters VA Med. Ctr., Bronx, NY; [3]Rehabil. and Human Performance, [4]Med., [5]Neurol., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Spinal cord injury (SCI) disrupts descending neural pathways that regulate cardiovascular (CV) and autonomic nervous system (ANS) function. Testosterone (T) plays a critical role in CV and ANS health; however, despite up to 50% of men with chronic SCI (≥1-year post-injury) exhibiting low T, T status is not routinely assessed in clinical SCI care. While ANS dysfunction is a well-recognized consequence of SCI, the relationship between ANS dysfunction and T deficiency remains poorly understood. Here, we examined cardiovagal (parasympathetic) responses to a cold face challenge (CFC) in four men (Age=40±14) with chronic cervical (n=2) or thoracic (n=2) traumatic SCI and confirmed hypogonadal status at baseline (BL). During the CFC, a validated probe of parasympathetic activity, continuous heart rate (HR) was recorded via 3-lead ECG and wavelet transformations were applied to examine the change in high-frequency heart rate variability (HF-HRV) from BL to post-intervention. Serum T profile biomarkers were assessed using liquid chromatography-mass spectrometry and equilibrium dialysis on blood samples taken during BL. Hypogonadism criteria included total T ≤300 ng/dL, free T ≤46 pg/mL, and/or bioavailable T ≤110 ng/dL with signs/symptoms of low T. Participants then completed one month of intranasal testosterone replacement therapy (iTRT). After iTRT, all serum T profile concentrations significantly increased from BL into the normal physiologic range (total T, 280±67 to 602±208 ng/dL; free T, 43±17 to 118±60 pg/mL; bioavailable T, 79±34 to 186±71 ng/dL; all $p < 0.01$). The small sample precluded statistical analysis; however, individual and group-level results are presented for the CFC. At BL, all four participants exhibited a paradoxical increased HR response to the CFC rather than an anticipated parasympathetic-mediated HR reduction. Following iTRT, all four participants demonstrated improved parasympathetic activity along with an attenuated rise in the HR in response to the CFC. These preliminary findings suggest that reduced endogenous T may disrupt parasympathetic ANS function and that iTRT may help restore parasympathetic reflex function in hypogonadal males with chronic traumatic SCI. Collectively, these results highlight the importance of early and routine T screening in clinical SCI care.

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Poster

PSTR356: Spinal Cord Injury: Human Monitoring and Interventions

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Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NICHD grant 1R03HD114768
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VA I01RX002474

Title: Effect of an auditory stimulus on lower limb muscles following spinal cord injury

Authors: *D. DE SANTIS[1], M. A. PEREZ[2];
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Abstract: Damage to descending motor pathways following incomplete spinal cord injuries (SCI) results in varying degrees of paralysis motor deficits in muscles below the level of the injury. Accumulating evidence suggests that the reticulospinal tract (RST) may be more susceptible to axonal plasticity and regeneration than the corticospinal tract and is likely largely implicated in the recovery of lower limb motor output after SCI. Brainstem circuits have dense connections with supraspinal centers and projects to a great diversity of spinal targets. However, despite the potentially fundamental role of the RST in mediating recovery, our ability to quantify and characterize reticulospinal modulatory input remains limited. RST neurons can be non-invasively engaged through brief loud acoustic stimuli (LAS), which have been used as conditioning stimuli to test RST effects on excitability. Facilitation of reflex responses in lower limb muscles following LAS has been well documented. However, the interactions between LAS and corticospinal responses in lower limb muscles are much less known. Here we evaluate the effect of a conditioning loud acoustic stimuli (LAS, 115dB) on the motor evoked potentials and soleus H-reflex activity evoked by transcranial magnetic stimulation in muscles of the in a group of uninjured individuals and in individuals with chronic incomplete SCI above T10.

Disclosures: D. De Santis: None. **M.A. Perez:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.01/Y11

Topic: B.09. Glial Mechanisms

Support: Merkin Peripheral Neuropathy and Nerve Regeneration (PNNR) Center Seed grant (25-DF/MG)

Title: Loss of monocarboxylate transporters suppresses reprogramming to repair Schwann cells in injured peripheral nerves

Authors: *S. SARKAR[1], I. ZHANG[2], A. HOKE[1], B. M. MORRISON[1];
[1]Neurol., Sch. of Medicine, Johns Hopkins Univ., Baltimore, MD; [2]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins University, Baltimore, MD, USA, Baltimore, MD

Abstract: Current surgical therapies for peripheral nerve injury are limited by slow axonal regrowth (~1 mm per day), prompting increased focus on understanding nerve regeneration mechanisms and developing effective strategies for accelerating nerve recovery. Schwann cells (SCs) are peripheral glial cells that myelinate axons and support axonal maintenance and regeneration. Previous research from our lab demonstrated that SC-specific ablation of monocarboxylate transporter 1 (MCT1), which is essential for transporting critical metabolites in cells, leads to hypomyelination and impaired lipid metabolism. However, nerve function and recovery remain largely unaffected due to the compensatory activity of MCT2 and MCT4. Preliminary data from transgenic mice with genetic deletion of all MCTs (e.g., MCT1, MCT2, MCT4; termed MCT triple KO mice) demonstrated a severe delay in nerve regeneration post-injury. SCs from MCT triple KO mice exhibited reduced lactate uptake, spare respiratory capacity, and compensatory glycolysis compared with wild-type controls. To better understand the function of MCTs, single-nucleus RNA sequencing was performed on uncrushed and 3- and 7-day crushed sciatic nerves from wild-type and MCT triple KO mice using the Illumina NovaSeq X platform. Day 3 was selected for maximal SC phagocytosis and day 7 for capturing early regeneration. Unbiased UMAP clustering identified distinct cell populations, including SCs (myelinating, non-myelinating, and repair), macrophages, fibroblasts, perineurial cells, endothelial cells, adipocytes, and muscle cells. MCT triple KO mice showed fewer repair SCs at 3 and 7 days after nerve crush than wild-type, indicating impaired adoption of this regenerative phenotype. Myelin Protein Zero (MPZ) was increased in both myelinating and non-myelinating SCs of MCT triple KO mice relative to wild counterparts. Since MPZ is normally downregulated during the switch to a repair phenotype, its increased expression suggests that SCs remain locked in a myelinating state, impairing nerve repair. In 3-day crushed MCT-deficient nerves, repair SCs showed increased RNA splicing and mRNA processing, but suppressed metabolism, differentiation, and structural pathways, resulting in a maladaptive response. By 7 days, despite activation of repair programs, downregulation of metabolic, immune, and phagocytic genes likely compromises myelination and nerve regeneration. Overall, these findings are poised to uncover regulatory pathways governing glial cell-mediated peripheral nerve degeneration/repair, identify key regulatory nodes, and highlight promising targets for future therapeutic development.

Disclosures: S. Sarkar: None. **I. Zhang:** None. **A. Hoke:** None. **B.M. Morrison:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.02/Y12

Topic: B.09. Glial Mechanisms

Title: Hybrid CNS-PNS glia participate in debris clearance after motor nerve injury in zebrafish

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Abstract: Axon regeneration following nerve injury relies on prompt debris clearance, primarily mediated by resident immune cells and domain-specific glia. This cleanup minimizes inhibitory signaling and inflammation that impede functional regrowth across both central (CNS) and peripheral nervous system (PNS) domains. While peripheral myelinating Schwann cells (SCs) act as highly plastic non-professional phagocytes with immunomodulatory roles, myelinating oligodendrocytes (OLs) of the CNS are comparatively less plastic with minimal involvement in debris clearance. This regenerative divide collides at motor exit point (MEP) transition zones (TZs), where efferent axons exit the spinal cord and myelination shifts from OL- to SC-mediated. A novel population of CNS-derived myelinating cells in zebrafish, known as MEP glia, migrates through these TZs in early development. Once in the PNS, MEP glia prevent the ectopic migration of OL-lineage cells out of the spinal cord through contact-mediated inhibition and competitively tile with SCs for myelination territory along motor axons. Following injury, these competitive dynamics may shift to cooperation if MEP glia facilitate repair. Supporting this, single-cell RNA sequencing data uncovered a unique transcriptomic signature for MEP glia in physiological developmental, enriched for genes associated with the innate immune system and blood-nerve barrier. Given their CNS origin, PNS localization, and hybrid transcriptomic profile we investigate whether MEP glia exhibit a response to injury characteristic of central or peripheral myelinating glia. Using two-photon laser ablation, we induce motor nerve damage in vivo near MEP TZs in larval zebrafish with concurrent acidic vesicle labeling and subsequent time-lapse imaging. MEP glia demonstrate debris engagement and uptake alongside SCs, with comparable response dynamics in the immediate hours post-injury. These findings identify MEP glia as an active participant in repair with a peripheral-like initial injury response alongside SCs, despite their CNS origin and retained identity in the PNS.

Disclosures: H. Murphy: None. **L. Fontenas:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.03/Y13

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Role of lysosome-related vesicles in motor neuron regeneration

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Abstract: Axon regeneration in the peripheral nervous system requires coordinated regulation of signaling pathways, intracellular transport, and local protein synthesis. Lysosomes contribute to these processes by regulating intracellular signaling and trafficking mechanisms that support the regenerative response following injury. Lysosomes and lysosome-related vesicles (LRVs) are increasingly recognized as dynamic signaling hubs, including for the mechanistic target of rapamycin (mTOR), a key regulator of cellular growth and protein synthesis. To investigate the relationship between lysosomal position and mTOR signaling, we focused on the BLOC-one-related complex (BORC), which regulates lysosomal positioning by linking LRVs to kinesin motors. Proper lysosomal positioning is essential for the spatial organization of signaling pathways within neurons. Disruption of BORC impairs lysosomal trafficking and neuronal function, without interrupting transport of other signaling molecules. Because mTOR activation occurs on lysosomal membranes, we hypothesized that impaired lysosomal transport would compromise injury-induced mTOR signaling and reduce regenerative capacity. We cultured human iPSC-derived motor neurons in Boyden chambers to physically separate the cell body from the axons. First, we examined mTOR pathway activation in soma and axonal fractions under basal conditions. Activation of the pathway was assessed by examining key mTOR signaling components and downstream effectors. BORCS7 KO did not significantly alter mTOR signaling activation. To investigate injury-induced signaling, axons were selectively injured by mechanical scraping of the axonal compartment while leaving neuronal cell bodies intact. Soma fractions were collected at multiple post-injury timepoints to capture the dynamic activation of mTOR. Together, these studies will determine whether BORC-dependent lysosomal positioning contributes to injury-induced mTOR signaling during axon regeneration.

Disclosures: M. Koppel: None. **S. Mahadik:** None. **C.E. Le Pichon:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.04/Y14

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: MIST RS-2024-00338713
MIST RS-2021-NR056922
MIST RS-2021-NR060088

Title: LRRK2 inhibition promotes peripheral axon regeneration via phosphorylation-network remodeling

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Abstract: Neurons in the central nervous system fail to regenerate after injury, whereas peripheral nervous system (PNS) neurons can regrow axons via activation of a pro-regenerative program. Although pathogenic mutations in leucine-rich repeat kinase 2 (LRRK2) are recognized as the primary genetic cause of Parkinson's disease, the physiological role of endogenous, non-pathogenic LRRK2 remains largely unknown. Here, we identify a previously unrecognized injury response of LRRK2 in the PNS and demonstrate its role in axon regeneration. We found that sciatic nerve crush injury (SNC) induces downregulation of LRRK2 mRNA and protein levels in dorsal root ganglia (DRGs). Notably, genetic depletion and pharmacological inhibition of LRRK2 enhanced regenerative axon growth and LRRK2 inhibition facilitated axonal mitochondrial trafficking in adult neuronal cultures. Furthermore, oral administration of LRRK2 inhibitors promoted sensory axon regeneration and accelerated functional restoration *in vivo* following SNC. Phosphoproteomic analyses comparing control and LRRK2 inhibitor-administered mice mapped distinct cellular processes and kinase-substrate signaling networks, revealing core kinases that drive this pro-regenerative state and mediate the LRRK2-dependent enhancement of mitochondrial transport. Together, our findings identify an endogenous, non-pathogenic role of LRRK2 and suggest that LRRK2 functions as an intrinsic suppressor of axon regeneration. These data support the potential repositioning of small-molecule LRRK2 inhibitors as therapeutic strategies to enhance peripheral nerve regeneration.

Disclosures: E. Yang: None. **E. Jang:** None. **S. Park:** None. **H. Choi:** None. **Y. Gim:** None. **E. Hur:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.05/Y15

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), Brazil

Title: Inosine reshapes the early proteomic and cellular response following sciatic nerve crush injury in mice

Authors: *R. CAVALCANTI[1], F. S. CARDOSO[1], T. TABOADA[1], D. DE ABREU PEREIRA[3], K. CARNEIRO[2], A. B. MARTINEZ[1], F. ALMEIDA[2];
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Abstract: Peripheral nerve injury triggers a complex repair program involving axonal degeneration, immune cell recruitment, and tissue remodeling. Inosine has been investigated as a potential neuroprotective and immunomodulatory molecule, however, its effects in the peripheral nervous system remain incompletely understood. In this study, we investigated the early response to compressive sciatic nerve injury in female C57BL/6 mice treated with inosine.

Animals were allocated to saline, inosine, or sham groups and followed after injury for different time points, with in vivo and proteomic analyses performed to evaluate tissue remodeling and molecular changes.
Preliminary proteomic analysis identified 148 proteins in the saline group and 264 proteins in the inosine group, with 97 proteins shared between both groups. Inosine-treated nerves showed enrichment of proteins associated with cellular morphogenesis, regulation of localization, multicellular organism development, cytosol, synapse, cell junction, L1CAM interaction, axonal guidance, protein metabolism, and immune and innate immune system pathways. In contrast, the saline group showed stronger representation of platelet activation, platelet degranulation, and hemostatic pathways.
In vivo analyses showed a higher number of myelin ovoids in the inosine group at 24 h and 48 h after injury, with mean values of 51.6 versus 33.3 at 24 h and 74.5 versus 56.0 at 48 h for inosine and saline, respectively. At 48 h, immunohistochemical quantification showed lower NFH and MBP signal in the inosine group and higher F480-positive cell counts, suggesting marked early structural remodeling and immune cell involvement in the injured nerve microenvironment.
Together, these findings suggest that inosine modulates the early response to peripheral nerve injury by shaping both proteomic and cellular events associated with axonal organization, myelin remodeling, and immune regulation. Ongoing analyses will further clarify the molecular mechanisms underlying inosine-mediated peripheral nerve repair.

Disclosures: R. Cavalcanti: None. **F.S. Cardoso:** None. **T. Taboada:** None. **D. De Abreu Pereira:** None. **K. Carneiro:** None. **A.B. Martinez:** None. **F. Almeida:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.06/Y16

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: MSCRF 2025-R2-MSCRFD-00024
Merkin PNNR Center 25 DF/C4/387
AAN Clinician Scientist Development Award
Als Scholars in Therapeutics Award

Title: Injury-Induced Axonal Translation of Importin β1 Promotes Human Motor Axon Regeneration

Authors: *A. TAGA[1], A. HOKE[2], N. J. MARAGAKIS[3];
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Abstract: Background: Local axonal protein translation has emerged as a mechanism enabling axonal regeneration. Prior studies in mouse and sensory neuron models highlight a distinct role

for axonal importin β1 (β1imp) in promoting regeneration after axotomy. However, the role of β1imp in human motor neurons, and whether it is a targetable pro-regenerative mechanism, remains underexplored. Methods: Control human iPSC-derived spinal motor neurons were cultured in 3-compartment microfluidic devices separating the cell body (CB), proximal axon (PA), and distal axon (DA). Axotomy was performed by vacuum aspiration of the DA compartment, and regeneration was assessed 48h later using linear Sholl analysis. β1imp RNA and protein levels were quantified by qPCR and WB before and after axotomy in each compartment. Local β1imp translation, axonal transport, and β1imp function were manipulated using peri-axotomy, axon compartment-restricted treatments with siRNA, ciliobrevin D, and ibetazol, respectively. β1imp was overexpressed by AAV transduction. Results: Under pre-axotomy conditions, β1imp protein was predominantly localized to the cell body, with minimal axonal expression. Following axotomy, β1imp protein increased markedly in axons. Peri-axotomy treatment of the axonal compartments with β1imp-targeting siRNA prevented this increase, supporting local axonal translation. In contrast, axotomy did not alter β1imp RNA levels in the cell body or axonal compartments, indicating that the protein increase was not driven by β1imp RNA trafficking into the axon. Axotomy also did not change somatic β1imp protein levels, and inhibition of axonal transport with ciliobrevin D did not affect post-axotomy axonal β1imp protein levels. Together, these findings suggest that axonal β1imp arises locally rather than through soma-to-axon trafficking. Linear Sholl analysis demonstrated that axonal β1imp knockdown with siRNA reduced axonal outgrowth after axotomy. Conversely, AAV-mediated β1imp overexpression enhanced axonal regeneration. Blocking axonal β1imp binding to nuclear localization signal (NLS)-containing cargo proteins with ibetazol reduced axonal regeneration, suggesting that β1imp promotes regeneration by engaging axonal injury signals destined for retrograde transport to the nucleus. Conclusion: Our preliminary work establishes axonal β1imp translation as a novel pro-regenerative mechanism in human motor neurons. Targeting β1imp may enhance axonal regeneration in peripheral neuropathy, nerve injury, and motor neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS).

Disclosures: A. Taga: None. **A. Hoke:** None. **N.J. Maragakis:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.07/Y17

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: RS-2025-25459402
RS-2025-16070516

Title: Transcriptome-based CMAP analysis reveals digoxin, a cardiac glycoside, as a potent agent that reprograms macrophages toward a pro-regenerative phenotype to support axonal regeneration

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Abstract: While central axons of dorsal root ganglia (DRG) neurons exhibit limited intrinsic regenerative capacity, their peripheral axons retain robust regenerative potential after injury. Our previous studies have underscored the critical role of DRG macrophages in enhancing the regenerative capacity of sensory neurons following peripheral nerve injury. However, the molecular signatures underlying these pro-regenerative macrophage phenotypes remain unclear. We established an in vitro neuron-macrophage interaction model to recapitulate the pro-regenerative macrophage phenotype and confirmed significant neurite outgrowth-promoting activity in macrophage-conditioned media (MCM). To identify molecular pathways associated with this phenotype, we performed bulk RNA sequencing of pro-regenerative macrophages induced in this model. We then used the Connectivity Map (CMAP), a perturbation-based gene expression database, to identify small molecules predicted to induce transcriptional profiles similar to those of pro-regenerative macrophages. Candidate compounds from the CMAP analysis were evaluated for neurite outgrowth-promoting activity in MCM using unbiased quantitative analysis with a high-content imaging system. Among the hit compounds, the cardiotonic steroid digoxin most significantly enhanced MCM neurite outgrowth activity and was therefore prioritized for mechanistic investigation. Transcriptomic profiling of digoxin-treated macrophages is being performed to identify key associated signaling pathways, followed by in vitro validation studies to elucidate the molecular mechanisms underlying digoxin-induced pro-regenerative macrophage phenotypes. This transcriptomics-guided approach provides a foundation for identifying therapeutic molecules and molecular pathways that reprogram macrophages toward pro-regenerative phenotypes, thereby promoting neuronal regeneration in neural injury and neurological disease.

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Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.08/Y18

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: ALRO – FAPESP Grant: 2023/02615-4
FAPESP Grant: 2024/09568-4

Title: Bioengineered PCL/GelMA Membranes and FGF2 Synergize with TEMPOL-PEG-Mediated Axonal Fusion to Enhance Peripheral Nerve Repair

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Abstract: Peripheral neurotmesis causes permanent functional deficits due to delayed regeneration. Although PEG-mediated axonal fusion rapidly restores nerve continuity, mechanical support is needed around the neurorrhaphy site to enhance the long-term stability of the repaired axons. We evaluated the antioxidant TEMPOL-PEG fusion (TMP fusion) and investigated its synergistic combination with a 3D bioprinted PCL/GelMA membrane loaded with thermostable fibroblast growth factor 2 (FGF2) to improve nerve repair. Adult female Lewis rats (n = 7 per group; Prot. No. 6775-1/2025) underwent sciatic nerve transection and were assigned to one of the following groups: neurorrhaphy (NRR), methylene blue-protected fusion (MB-fusion), TMP fusion, TMP fusion with a PCL/GelMA membrane (TMP + Mem), or TMP fusion with a membrane plus FGF2 (TMP + Mem + FGF2). Sensorimotor recovery was evaluated via CatWalk gait analysis (peroneal function index [PFI] and step sequence) over 8 weeks, and electrophysiological recovery was evaluated via compound muscle action potentials (CMAPs). Axonal integrity and spinal cord glial responses and synaptic preservation were assessed using immunofluorescence, while scaffold integration was characterized via scanning electron microscopy (SEM). TMP-fusion significantly improved outcomes compared to NRR by week 8 (PFI, $p=0.0232$; step sequence, $p=0.0499$; CMAPs amplitude, $p=0.0002$). The histology of the TMP-fusion group revealed enhanced axonal preservation (anti-neurofilament, $p<0.0001$; S100, $p=0.0004$), reduced glial activation (anti-Iba-1, $p=0.0035$; GFAP, $p=0.001$), and superior spinal cord synaptic integrity (synaptophysin, $p<0.0001$). Crucially, integrating the 3D bioprinted membrane accelerated functional recovery, with FGF2 yielding the close-to-normal outcomes. Both the TMP+Mem and TMP+Mem+FGF2 groups exhibited significant improvements over NRR in PFI ($p=0.0037$ and $p=0.0008$) and step sequence ($p=0.0443$ and $p=0.0456$), respectively. Electrophysiologically, the FGF2-supplemented group significantly outperformed the membrane-alone group (CMAPs, $p<0.0001$ vs. $p=0.0006$). Such functional superiority was confirmed by SEM at 8 weeks, demonstrating enhanced scaffold integration and extracellular matrix organization in the TMP+Mem+FGF2 group, characterized by a dense fibrillar collagen network, whereas scaffolds without FGF2 exhibited less organized tissue remodeling. Overall, the present study demonstrates the efficacy of combining PEG fusion with 3D-bioprinted scaffold support, which may be in turn translated to future medical use.

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Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.09/Y19

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), Brazil
FAPERJ
CNPq

Title: Therapeutic Effects of Platelet-Rich Plasma on Sciatic Nerve Regeneration following transection injury and repair with polylactic acid conduits in Mice

Authors: G. SANTOS[1], F. S. CARDOSO[3], J. BROCOLO FERNANDES[1], L. D. HERINGER[4], A. B. MARTINEZ[2], *F. M. ALMEIDA[1];
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Abstract: Peripheral nervous system (PNS) injuries are a major clinical challenge and frequently result in motor and sensory impairments. Although peripheral nerves retain an intrinsic regenerative capacity, recovery after severe injuries such as nerve transection is often incomplete. Biomaterials, including polylactic acid (PLA), have been developed to support axonal regeneration, while Platelet-Rich Plasma (PRP) has attracted considerable interest due to its high concentration of growth factors with regenerative, angiogenic, and anti-inflammatory properties. The present study investigated the effects of PRP on sciatic nerve regeneration in a mouse model of transection injury repaired using PLA tubulization. Male and female C57BL/6 mice (8-10 weeks old) underwent sciatic nerve transection followed by reconstruction with PLA conduits. Animals were allocated into two experimental groups: Saline + PLA and PRP + PLA. PRP was directly administered into the conduit during surgery. Functional recovery was evaluated through the Sciatic Functional Index (SFI), Pinprick sensory testing, and electrophysiological analyses. Morphological assessment was performed using semithin sections of regenerated nerves, while gastrocnemius muscle weight was measured to evaluate muscle preservation and denervation-induced atrophy. Both groups exhibited marked motor and sensory deficits after injury. However, animals treated with PRP showed significantly improved functional recovery, with superior SFI scores from the third postoperative week onward. Sensory recovery was also accelerated and more consistent in the PRP-treated group, as demonstrated by the Pinprick test. Electrophysiological recordings revealed higher compound muscle action potential (CMAP) amplitudes in PRP-treated animals, indicating enhanced nerve conduction and regeneration. Histological analyses demonstrated larger nerve caliber, increased fiber density, and greater vascularization in regenerated nerves from the PRP group. In addition, the muscle index, calculated from the ratio between ipsilateral and contralateral gastrocnemius muscle weights, showed reduced muscle atrophy in PRP-treated animals. These findings demonstrate that PRP enhances sciatic nerve regeneration following transection injury, promoting motor and sensory recovery, greater preservation of muscle mass, and superior morphological outcomes. The results highlight the therapeutic potential of PRP as an strategy for peripheral nerve repair and suggest its usefulness in reducing the functional consequences of muscle denervation after severe PNS injuries.

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Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.10/Y20

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Therapeutic Ultrasound and Andrographolide Promote Peripheral Nerve Regeneration and Functional Recovery Following Sciatic Nerve Injury

Authors: *B. P. SUATO[1,2];
[1]Anat., Mahidol Univ., Bangkok, Thailand; [2]Div. of Physical Therapy, Fac. Allied Hlth. Sci., Burapha Univ., Chonburi, Thailand

Abstract: Therapeutic Ultrasound and Andrographolide Promote Peripheral Nerve Regeneration and Functional Recovery Following Sciatic Nerve InjuryAuthors B.P. SUATO[1,4], N. JONGAPIRATTANAKUL[1], K. BAMRUNGSUK[2], W. DACHARUX[1], C. TURBPAIBOON[1], A. SIRIPORN[3], S. CHOMPOOPONG[1*1]Dept. of Anatomy, Fac. Med. Siriraj hosp., Mahidol Univ., Bangkok, Thailand; [2]Dept. Basic Med. Sci., Fac. Med. Vajira Hos., Navamindradhiraj Univ., Bangkok, Thailand; [3]Dept. Physical Therapy, Fac. Allied Health Sci., Chulalongkorn Univ., Bangkok, Thailand; [4]Div. of Physical Therapy, Fac. Allied Hlth. Sci., Burapha Univ., Chonburi, Thailand
DisclosuresB.P. SUATO: None. N. JONGAPIRATTANAKUL: None. K. BAMRUNGSUK: None. W. DACHARUX: None. C. TURBPAIBOON: None. A. SIRIPORN: None. S. CHOMPOOPONG: None.
AbstractPeripheral nerve injuries often result in incomplete recovery despite surgical repair. Therapeutic ultrasound (US) promotes peripheral nerve regeneration, while andrographolide (ANDRO), a diterpenoid with anti-inflammatory and neuroprotective properties, may enhance recovery. This study investigated the effects of US with or without ANDRO on nerve regeneration, muscle preservation, and functional recovery after sciatic nerve injury using the stepwise transection and fibrin glue (STG) rat model. Adult Sprague-Dawley rats were assigned to SH, SNI, SNI+ANDRO, SNI+US, and SNI+US+ANDRO groups. ANDRO was administered intraperitoneally (1 mg/kg, three times weekly for 2 weeks). US treatment (1 MHz, 140–250 mW/cm², 5 min/day, 5 days/week) was applied for 6 weeks. Functional recovery was assessed using the sciatic functional index (SFI). At 6 weeks post-injury, sciatic nerves and hindlimb muscles were harvested for histological analysis. Axon diameter, fiber diameter, myelin thickness, muscle wet weight, and muscle CSA were evaluated. ANDRO significantly improved axon diameter, fiber diameter, myelin thickness, muscle wet weight, CSA, and functional recovery. US also enhanced nerve morphology and SFI recovery compared with untreated injured animals. Although combined US+ANDRO improved functional outcomes and attenuated muscle atrophy, its effects were not significantly greater than individual treatments, suggesting

no synergistic interaction. This is the first study to evaluate combined therapeutic ultrasound and andrographolide treatment in the STG peripheral nerve injury model. Both interventions promoted peripheral nerve regeneration and functional recovery, supporting their potential for peripheral nerve repair.**Keywords:** Peripheral nerve regeneration; Therapeutic ultrasound; Andrographolide; Sciatic nerve injury; Functional recovery

Disclosures: B.P. Suato: None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.11/Y21

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: DoD HT9425-24-1-0170

Title: Functional and neuroanatomical outcomes of Nerve Tape-repaired peripheral nerve injuries with nerve end separation

Authors: *E. A. HIBBARD, J. METER, O. LEPAGE, G. BENDALE, J. ISAACS; Virginia Commonwealth Univ., Richmond, VA

Abstract: End-to-end approximation of severed nerve stumps is the ideal outcome of surgical nerve repair but is not always clinically practical. For instance, end-to-end repairs with substantial tension across the site of coaptation are associated with ischemia, intraneural hemorrhaging, and scar formation. Solutions for relieving tension, e.g., autografts and decellularized allografts, have associated risks including donor site morbidity and rejection. Nerve Tape is a novel coaptation device that uses embedded Nitinol microhooks within laminated layers of decellularized porcine small intestine submucosa to stabilize, entubulate, and protect severed nerve ends. Nerve Tape provides a unique opportunity to investigate the impact of slight gapping between nerve ends during surgical repair in order to relieve tension without nerve grafts. In the current study, we examined the potential effects of minor nerve end separation with Nerve Tape repair on both sensory and locomotor recovery, as well as muscle strength and motor reinnervation outcomes. Young adult male Lewis rats were given a unilateral sciatic nerve injury repaired with Nerve Tape (BioCircuit Technologies). During repair, nerve stumps were engaged into the Nitinol microhooks in a manner that left either a 2mm or 5mm gap between nerve ends, or resulted in normal end-to-end repair, i.e., no gap. Locomotor and sensory behavioral testing were performed every other week postoperatively. At 12 weeks post-injury, motor strength testing was performed bilaterally to the gastrocnemius muscles, then muscles were harvested for assessment of mass and girth. To evaluate motor reinnervation pattern, motoneurons whose axons had regenerated into the flexor digitorum brevis muscle were retrogradely labeled with cholera toxin-conjugated horseradish peroxidase (BHRP). The functional outcomes of nerve injury including locomotor recovery and gastrocnemius contractile

strength showed no differences between groups. Slight nerve end separation also did not induce pro-nociceptive effects compared to animals with traditional end-to-end repairs. BHRP labeling showed that all animals exhibited some regeneration to the most distal sciatic-mediated muscle, regardless of repair type. Importantly, animals with 5mm gapped injuries exhibited significantly smaller gastrocnemius muscles ipsilateral to the injury compared to animals without gaps. These results suggest that traditional end-to-end approximation is the appropriate technique for the application of Nerve Tape devices.

Disclosures: E.A. Hibbard: None. **J. Meter:** None. **O. LePage:** None. **G. Bendale:** None. **J. Isaacs:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.12/Y22

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: CDMRP W81XWH-20-1-0854
NIH 1R15NS140947-01A1
C.H. Leach II Fund
NSF DBI-1726368
NIH R15 GM104876-03S1

Title: Radial nerve transection in Macaque (Macaca fascicularis) treated with a macrophage targeted immunomodulatory nanotherapeutic improves voluntary engagement and accelerates nerve regeneration.

Authors: *J. A. POLLOCK[1], V. S. GORANTLA[3], J. M. JANJIC[2];
[1]Biol. Sci., [2]Sch. of Pharm. & Grad. Sch. of Pharmaceut. Sci., Duquesne Univ., Pittsburgh, PA;
[3]Inst. for Regenerative Med., Advocate Hlth., Winston-Salem, NC

Abstract: Modeling nerve injury in adult Macaque (NHP) with unilateral radial nerve transection and repair, was used to evaluate the efficacy of the Long-Acting Nanoemulsion Analgesic (LANA). An immunomodulatory therapeutic nanoemulsion with the NSAID celecoxib and near infrared dye Indocyanine green (ICG).Used as a single perioperative treatment delivered i.v. during the radial nerve transection and repair, the nanodroplets are phagocytosed by circulating monocytes that then naturally accumulate at the injury. Treating both males and females, animals were assessed in comparison to animals receiving drug-free nanoemulsion followed by the standard of care (SOC: i.m. meloxicam daily).The nanoemulsion near-infrared fluorescence (NIRF) imaged with a Fluobeam System reveals the accumulation of the ICG, a direct surrogate of the degree macrophage associated inflammation[1-7]. LANA treatment resulted in significant reduction of inflammation in the NHP forearm.LANA also produced sustained control of hypersensitivity as observed through voluntary behaviors of

reaching and grabbing. Compared to the drug-free nanoemulsion SOC animals exhibited persistent guarding, reduced engagement with their hand, and inability to generate a functional grasp.Electrophysiological assessment used electrically evoked peripheral nerve potentials recorded upstream and downstream of the repair site to quantify peak latency, peak amplitude, and calculated conduction velocity. LANA treatment resulted in significant enhanced recovery as compared to SOC with a clear sex difference; male recovery was advanced compared to females. We observe a similar sex difference has been previously observed in rodent injury models treated with a celecoxib nanotherapeutic[2,3,5].We demonstrate that 6 weeks post-surgery, nerve biopsy from the site of injury exhibited the presence of ICG NIRF by whole tissue imaging. We then demonstrated the presence of the nanotherapeutic in M2 phenotypic anti-inflammatory macrophages in histological sections stained for CD68 and TFRC followed by confocal microscopy.Our interpretation is that the long-lasting presence of the nanotherapeutic in the resident M2 macrophages enhances healing and regeneration. **References:**1 Balogh et al 2022 Antiox & Redox Sig **36**(1-3): 122-1432 Deal et al 2023 Int J Mol Sci **24**(11): 91633 Deal et al 2022 Sci Rep **12**(1): 84724 Janjic et al 2018 J Neuroimmunol **318**: 72-795 Liu et al 2020 Theranostics **10**(4): 16946 Saleem et al 2019 Acta Neuropathol Commun **7**(1): 1087 Vasudeva et al 2014 PLoS One **9**(2): e90589

Disclosures: J.A. Pollock: None. **V.S. Gorantla:** None. **J.M. Janjic:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.13/Y23

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: R01 GM155523

Title: Activation of Nav1.8-expressing Sensory Neurons Delays Facial Burn Wound Healing

Authors: M. SUEHIRO, D. PAVLENKO, *T. AKIYAMA;
Univ. of Miami, Miami, FL

Abstract: Background: Recent studies have highlighted the critical role of crosstalk between sensory neurons and immune cells in wound healing. However, the precise contribution of Nav1.8-expressing sensory neurons to the pathophysiology of wound healing remains fully elucidated. In this study, we investigated whether chemogenetic activation of Nav1.8-expressing sensory neurons affects facial burn wound healing and the local inflammatory microenvironment. Methods: We utilized a chemogenetic approach by selectively expressing excitatory DREADD in Nav1.8-positive neurons in mice. To chronically activate Nav1.8-positive neurons, the selective DREADD agonist JHU37160 was topically applied to the cheek twice daily in both male and female Cre+ mice and their littermate controls. Standardized burn wounds were induced on the cheek, and wound healing was monitored by digital photography

before injury and on days 1, 3, 5, 7, 10, 14, and 21 post-burn. Wound area was quantified using ImageJ software, and wound closure rates were calculated over time. In separate cohort of mice, cheek skin samples were collected on days 3, 5, and 7 following burn injury. Tissue samples were subsequently analyzed by cytokine array and immunohistochemistry to characterize changes in the local inflammatory microenvironment. Results: Chemogenetic activation of Nav1.8-positive neurons significantly delayed facial burn wound closure between days 3 and 7 post-injury in male Cre+ mice compared to the control group. In contrast, no significant differences in the healing rate were observed in female mice, indicating a sex-specific effect. Cytokine array analysis of wound tissue revealed marked alterations in the expression of myeloperoxidase (MPO) and lipocalin-2, indicating prolonged and excessive inflammation. Conclusion: Chemogenetic activation of Nav1.8-positive sensory neurons triggers a sex-specific delay in facial burn wound healing during the early inflammatory phase. This neural-driven delay is characterized by an altered inflammatory microenvironment involving MPO and lipocalin-2. These results reveal a critical role for Nav1.8-expressing sensory neurons in regulating burn wound repair and suggest that neuroimmune pathways may offer novel therapeutic strategies for wound healing.

Disclosures: M. Suehiro: None. **D. Pavlenko:** None. **T. Akiyama:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.14/Y24

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH AI093504
NIH AI197853
HDTRA1-22-1-0029

Title: A Tunable Strategy to Counteract Off-Target BoNT/A Adverse Effects Without Disrupting Therapeutic Paralysis

Authors: *T. WENTZ[1], S. O'BRIEN[1], B. GREGG[2], S. AHMAD[3], P. M. MCNUTT[4]; [1]WFIRM, Winston-Salem, NC; [2]WFIRM- Wake Forest Inst. for Regenerative Med., Winston Salem, NC; [3]Wake Forest Inst. for Regenerative Med., Winston Salem, NC; [4]Wake Forest Inst. for Reg. Med., Wake Forest Sch. of Med., Trinity, NC

Abstract: Intramuscular injection of botulinum neurotoxins (BoNTs) produces localized and reversible chemodenervation and forms the basis of widely used therapeutics such as onabotulinumtoxinA. Although generally safe, unintended spread of BoNT beyond the target muscle can occur due to intrinsic muscle physiology, dosing error, or patient specific comorbidities, leading to systemic botulism like symptoms. We previously demonstrated that systemic administration of 3,4 diaminopyridine (3,4 DAP), an FDA approved Kv channel

antagonist, reverses clinical signs of systemic botulism. Here, we show that carefully titrated 3,4 DAP dosing can selectively counteract off target BoNT/A effects while preserving the desired paralysis of the injected muscle. Mice receiving intramuscular 1.25 LD50 BoNT/A in the extensor digitorum longus exhibited robust local paralysis accompanied by clinical signs of systemic botulism, including respiratory weakness. Daily subcutaneous 3,4 DAP at ≥0.5 mg/kg significantly reduced both systemic signs of botulism and hindlimb paralysis, indicating global antagonism of BoNT/A. In contrast, daily 3,4 DAP doses ≤0.25 mg/kg produced a significant reduction in systemic signs without altering BoNT/A induced hindlimb paralysis. Dose escalation studies revealed that 3,4 DAP and BoNT/A are mutually titratable: 3,4 DAP doses that were ineffective against 1.25 LD50 BoNT/A became effective once the intramuscular BoNT/A dose was reduced to 0.5 or 0.25 LD50. To test selective therapeutic effects in a translational model, rats were challenged with 1.25 LD50 BoNT/A injected into the gastrocnemius muscle and given vehicle or 3,4 DAP (1 mg/kg·h) via a subcutaneous catheter. Continuous 3,4 DAP infusion significantly improved mobility and reduced systemic signs without diminishing hindlimb paralysis relative to vehicle controls. These findings identify 3,4 DAP as a tunable adjunct therapy capable of mitigating off target BoNT/A toxicity while maintaining the clinically beneficial targeted paralysis. This titratable pharmacological approach may improve the safety profile of therapeutic BoNT/A use, particularly in patients at elevated risk for toxin spread.

Disclosures: T. Wentz: None. **S. O'Brien:** None. **B. Gregg:** None. **S. Ahmad:** None. **P.M. McNutt:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.15/Y25

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Intramural NICHD: #ZIA-HD008966

Title: IRP2 maintains neuronal iron homeostasis, and its loss causes iron-dependent neurodegeneration

Authors: *B. S. MIETTO[1,2], N. MAIO[3], D. ZHANG[3], A. STAVSKY[5], C. E. LE PICHON[4], T. ROUAULT[6];
[1]NIH / NICHD, Washington, DC; [2]UFJF, Juiz de Fora, Brazil; [4]NIH, [3]NIH, NICHD, Bethesda, MD; [5]Natl. Inst. of Hlth., Bethesda, MD; [6]NICHD, NIH, Bethesda, MD

Abstract: Iron regulatory proteins (IRPs) coordinate intracellular iron homeostasis by controlling the translation or stability of iron-responsive element-containing mRNAs. IRP1 and IRP2 are ubiquitously expressed in the nervous system. Loss of IRP1 fails to produce neurological phenotypes while IRP2 deficiency causes neurodegeneration in humans and mice, with axonopathy and regional iron accumulation as key features, positing IRP2 as the main iron

regulator in neurons. Yet, how IRP-dependent iron regulation is organized across neuronal compartments remains poorly defined, particularly in axons that depend heavily on mitochondrial metabolism and local translation, both of which are iron-dependent processes. Here, we investigated compartment-specific iron regulation in human neurons and mouse peripheral nerves. We found that axons contain a broad range of iron regulatory machinery, including transcripts and proteins involved in iron uptake, storage, Fe-S cluster biogenesis, and heme metabolism. Functional analyses revealed that IRP2 is the dominant regulator of this machinery, while IRP1 is predominantly maintained in its aconitase form, with limited contribution to neuronal iron regulation. Consistent with this, iron depletion or supplementation with DFO or FAC robustly modulated IRP2-IRE binding, with minimal engagement of IRP1-IRE activity. Loss of IRP2 disrupted IRP-IRE regulation, leading to increased ferritin expression, reduced transferrin receptor expression, and redistribution of intracellular iron away from bioavailable pools. These defects impaired mitochondrial function and compromised axonal integrity. Notably, pharmacologically enhancing IRP1-IRE activity in neurons with Tempol recovered neuronal iron regulation, intracellular iron availability, and mitochondrial performance, ultimately preserving axonal integrity. Together, these findings identify IRP2 as the dominant neuronal iron regulator and support a model in which IRP2 loss drives iron-dependent neurodegeneration. Our work also establishes IRP1-IRE activation as a rational therapeutic strategy to restore neuronal iron homeostasis and axonal integrity.

Disclosures: B.S. Mietto: None. **N. Maio:** None. **D. Zhang:** None. **C.E. Le Pichon:** None. **T. Rouault:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.16/Y26

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NSF 2215401
NIH T32GM139787
NIH T32GM007267

Title: Uncovering peripherin-dependent injury responses in sensory neuron subpopulations

Authors: *I. C. SWANN[1], M. LU[2], E. STEPANOVA[3], C. DEPPMANN[2], E. ZUNDER[5], B. R. WINCKLER[4];
[1]Cell & Developmental Biol., [2]Univ. of Virginia, Charlottesville, VA; [3]Biol., Univ. of Virginia, Crozet, VA; [4]Cell Biol., Univ. of Virginia, Earlysville, VA; [5]Biomed. Engin., Univ. of Virgina, Charlottesville, VA

Abstract: Intermediate filaments (IFs) constitute a highly conserved superfamily of ubiquitous, cell-specific cytoskeletal proteins. In neurons, up to ten different IFs are involved in many

essential processes, like developmental axon outgrowth, axon caliber/integrity, and injury signaling. Remarkably, while all neurons express IFs, different types of neurons express different combinations of IFs; these highly regulated expression patterns ("IF codes") imply specific roles for each IF that are yet to be uncovered. One subtype, peripherin (PRPH), is expressed primarily in the peripheral nervous system and upregulated coincidently with developmental axon outgrowth and during axon regeneration after injury. Mutations in PRPH are linked to several degenerative nerve diseases, such as peripheral neuropathies and amyotrophic lateral sclerosis. Still, how PRPH contributes to normal neuronal physiology and pathophysiology is unknown. We hypothesize that peripherin is a necessary component of IF networks of developing and regenerating dorsal root ganglion (DRG) neurons. Here, we utilize imaging mass cytometry, a multiplexed spatial proteomics technique with subcellular resolution, to visualize 10 IFs simultaneously in mouse sensory neurons of the DRG. Results: Using 15+ well-established cell identity markers, we first define comprehensive "IF codes" of the major DRG sensory neuron subtypes in embryonic, postnatal, and adult WT and PRPH KO mice. We observe that all WT and PRPH KO DRG neurons express at least one IF required for mature network formation (i.e., PRPH, α-internexin, and neurofilament L). In PRPH KO DRG, however, we observe broad decreases in neuronal IF immunoreactivity and alterations in the spatial densities of some DRG neuron subtypes. We propose that surviving PRPH KO neurons maintain competent IF networks into adulthood through the redundant expression of either α-internexin or neurofilament L. Finally, we again employ IMC to test the hypothesis that PRPH is necessary for nerve injury responses. One day after sciatic nerve transection, we observe a reduction in the proportion of ATF3+ neurons in PRPH KO DRG relative to WT. Ongoing studies seek to expand upon this work and understand how PRPH may contribute to regenerative responses after sciatic nerve crush.

Disclosures: I.C. Swann: None. **M. Lu:** None. **E. Stepanova:** None. **C. Deppmann:** None. **E. Zunder:** None. **B.R. Winckler:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.17/Y27

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Grant R01NS140664

Title: Nodes of Ranvier are sites of neurofilament accumulation in a mouse model of Charcot-Marie-Tooth disease type 2E

Authors: *H. BAILEY, P. MONSMA, A. BROWN;
The Ohio State Univ., Columbus, OH

Abstract: Neurofilaments (NFs) are abundant polymers in axons that are required for the growth of axon caliber, influencing conduction velocity. NFs assemble in the nerve cell body and are transported into axons along microtubule tracks. NFs are normally distributed uniformly along axons but in many neurotoxic conditions and neurodegenerative diseases, the filaments are depleted from some regions and accumulate excessively in others, leading to axonal atrophy and swellings which suggest an impairment in NF transport. One such disease is Charcot-Marie-Tooth disease type 2E (CMT2E), which is caused by mutations in NF protein L (NFL). We are using immunofluorescence array tomography to characterize the redistribution of axonal NFs in a genetically authentic knock-in mouse model of CMT2E heterozygous for the N98S mutation in NFL (N98S/+). Immunofluorescence array tomography is a light microscopic serial sectioning technique that yields volumetric information with isometric diffraction-limited resolution in all three dimensions. We are focusing on neurons of the dorsal root ganglia (DRG) because of their stereotyped and relatively simple morphology. In wild type mice, 100% of myelinated axons contain abundant NFs, extending throughout their length within the DRG and into the dorsal root and spinal nerve. In CMT2E mice, only 15% of myelinated axonal profiles contain abundant NFs in the DRG and this drops to 7% in axons emerging from the ganglion. Intriguingly, these NF-rich axonal profiles all show a dramatic segregation of NFs from their microtubule tracks. Whereas NFs and microtubules are normally interspersed throughout the axonal cross-section in healthy axons, the microtubules in the CMT2E axons cluster into what is typically a central island, with the NFs displaced to the axonal periphery. Of the NF-rich axonal profiles, 18% are swollen with thinned myelin and large accumulations of NFs. Remarkably, 84% of these accumulations are found immediately adjacent to one side of a node of Ranvier. In one third of these, we were able to determine the orientation of these axons, and the swellings were always on the proximal side. This is interesting because myelinated axons are constricted at nodes of Ranvier and we have shown previously that NFs must accelerate locally to navigate this bottleneck. We speculate that nodal constrictions are an impediment to the movement of NFs in the CMT2E mice, resulting in NF accumulations in the proximal internodes and depletion distally. Thus, the absence of NFs in the distal axons may reflect upstream pileups at nodes of Ranvier and this may explain the selective vulnerability of myelinated axons to NF accumulations in disease.

Disclosures: H. Bailey: None. **P. Monsma:** None. **A. Brown:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.18/Y28

Topic: B.09. Glial Mechanisms

Support: R01NS146225 to YP, SB and JS
TEADCMT1A to YP and SB

Title: A New Way to Control PMP22 in CMT1A

Authors: *A. S. MONDSCHEIN[1], K. M. EYER[2], R. JOHNSON[2], K. PANCHAL[2], O. HARRIS[2], J. P. SVAREN[4], S. BELIN[2], Y. POITELON[3];
[1]Neurosci. & Exptl. Therapeut., [3]Dept. of Neurosci. and Exptl. Therapeut., [2]Albany Med. Col., Albany, NY; [4]Waisman Ctr., Univ. Wisconsin-Madison, Madison, WI

Abstract: Charcot-Marie-Tooth disease type 1A (CMT1A), the most common inherited peripheral neuropathy, is driven by overexpression of the myelin protein PMP22, leading to progressive demyelination, muscle weakness, and sensory loss. Despite a well-defined genetic mutation, current treatments remain limited to symptomatic management, highlighting the need for strategies that directly target disease mechanisms. Recent advances have identified TEAD transcription factors as regulators of PMP22 expression, positioning this pathway as a potential therapeutic entry point. Small-molecule inhibitors of TEAD activity are already in clinical development for cancer, raising the possibility of repurposing these compounds for inherited neuropathies.Here, we tested whether pharmacological inhibition of TEAD can modulate PMP22 expression in Schwann cells. TEAD inhibition altered the expression of PMP22 and canonical TEAD target genes, supporting a functional link between TEAD activity and PMP22 regulation. Notably, the effects were sensitive to treatment conditions, suggesting that TEAD-dependent control of PMP22 is dynamic and context-dependent.Together, these findings highlight TEAD signaling as a druggable regulator of PMP22 and support TEAD inhibition as a potential disease-modifying strategy for CMT1A. Ongoing work aims to define the therapeutic window of this approach and to determine whether reducing PMP22 levels can restore myelination and improve nerve function in vivo.

Disclosures: A.S. Mondschein: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Vivance Theraputics, Charcot-Marie-Tooth association, National Institute of Neurological Disorders and Stroke, peripheral nerve society. **K.M. Eyer:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Vivace Therapeutics, NINDS, Charcot-Marie-Tooth association, Peripheral Nerve Society. **R. Johnson:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Vivace Therapeutics, Charcot-Marie-Tooth Association, Peripheral Nerve Society, NINDS. **K. Panchal:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Vivance Theraputics, NINDS, peripheral nerve society, Charcot-marie-tooth association. **O. Harris:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Vivace therapeutics, NINDS, Peripheral Nerve Society, Charcot-marie-tooth association. **J.P. Svaren:** None. **S. Belin:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Vivace therapeutics, Charcot-Marie-tooth association, Peripheral Nerve Society, NINDS. **Y. Poitelon:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Vivace therapeutics, NINDS, Peripheral Nerve society, Charcot-Marie-Tooth association.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.19/Y29

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Therapies for Inherited Neuopathies

Title: Molecular markers associated with the disease progression of Charcot-Marie-Tooth disease type 1X (CMT1X) as potential tools to identify new therapies.

Authors: A. GHAVAMI[1], J. REPASS[2], M. KWAN[1], J. BELTRAN[1], T. HANANIA[1], ***M. A. SCHEIDELER**[3];
[1]PsychoGenics, Inc., Paramus, NJ; [2]ARQ Genet. LLC, Bastrop, TX; [3]HumanFirst Therapeut. LLC, Silver Spring, MD

Abstract: The Hereditary Peripheral Neuropathies, collectively known as Charcot-Marie-Tooth (CMT) disorders, represent as a group one of the most prevalent of rare neurological diseases, with an incidence in the population of 1:2500. There are presently no available therapeutic options for patients, who experience progressive and debilitating loss of limb function due to muscle atrophy, and in some instances, sensory loss. This is attributable to progressive demyelination of peripheral nerve, and axonal degeneration. The Type 1 CMT disorders are the largest patient group, each disorder characterized by a defect in a gene critical for normal myelination, or its normal expression. CMT1X is caused by mutation in the *gjb-1* gene encoding the Connexin 32 gap junction channel on the cell surface of Schwann cells. This CMT disorder is an attractive therapy target due to a well described understanding of how the pathology can be regulated (Klein et al., 2015), and structure-function relationships established using patient mutations (Qi et al., 2023). The best-known mouse model of CMT1X is deficient in *gjb-1* gene expression (Nelles et al., 1996), and replicates key aspects of the disease pathology (Klein et al., 2015). Changes in grip strength, as well as electrophysiological and histological changes characteristic of the disease, become significant as animals age and are fully evident within 8-12 months of age. In order to expand available outcome measures, a study was made of molecular markers likely to be affected in neurodegenerative and demyelination disorders. To this end, a panel of markers associated with neurodegeneration and demyelination was evaluated by qPCR in peripheral nerve samples, as potential surrogate measures of disease progression. An additional goal of the work is to further accelerate the timelines needed for therapy evaluation in the CMT1X mouse, and establish markers that would be suited for use in young animals to monitor target engagement reflecting therapeutic treatment, and before disease pathology is evident. Neurofilament light (NfL) assays, performed in CSF and in serum samples, showed that significant disease marker effects can be measured in mice at 8wks of age. This compares with measures of grip strength, an early functional outcome measure of disease pathology, which begin to show a significant deficiency at 14 wks of age that is only fully evident at 20 wks of age.

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Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.20/Y30

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: funded by Charcot Marie Tooth Association

Title: Refining ultrastructural endpoints for CMT1X therapeutic studies using Gjb1-null mice and high throughput EM.

Authors: E. K. BENSON[1], M. A. SCHEIDELER[2], ***G. J. KIDD**[1];
[1]Cleveland Clin. Res., Cleveland, OH; [2]HumanFirst Therapeut. LLC, Silver Spring, MD

Abstract: X-linked Charcot-Marie-Tooth disease type 1 (CMT1X) is the second most common hereditary peripheral neuropathy and results from mutations in the GJB1 gene (gap junction protein connexin 32). GJB1-null mice express many aspects of the human CMT1X phenotype, including ultrastructural changes that may be earliest and most sensitive markers of disease. To facilitate exploratory studies of potential therapies, we investigated entire transverse sections of fixed femoral and sciatic nerves from GJB1-null (het) and WT mice, imaged at high resolution (10nm/pixel) using array tomographic scanning electron microscopy. Several potential primary endpoints were identified. In the GJB1-null het mouse (6 months old), we documented substantial increases in (a) swelling of the periaxonal space consistent with disrupted gap junctions; (b) large diameter unmyelinated and thinly myelinated axons; (c) degenerating myelin profiles; (d) phagocytic macrophages with myelin debris indicative of myelin degeneration; and (e) onion bulb structures indicative of cycles of demyelination/remyelination. Diameter-based filtering indicated substantial therapeutic windows in which to measure efficacy with as few as 3 WT and 5 GJB1-null mice. Potential therapies may encompass multiple strategies, such as gene-replacement, inhibiting myelin degeneration, and reducing inflammation. The ultrastructural endpoints identified here permit testing of multiple approaches.

Disclosures: E.K. Benson: None. **M.A. Scheideler:** None. **G.J. Kidd:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.21/Y31

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: ARPA-H

Title: Electrical Impedance Tomography Detects Peripheral Nerve Structural Changes Relevant to Diabetic Neuropathy

Authors: *P. PAHLAVAN[1], J.-M. C. BOUTEILLER[3], K. K. GOKOFFSKI[4], G. LAZZI[2]; [1]Electrical Engin., [2]Electrical Engineering, ophthalmology, Biomed. engineering, USC, Los Angeles, CA; [3]Biomed. Engin., USC / INDRC, Los Angeles, CA; [4]ophthalmology, Univ. of California, Irvine, Irvine, CA

Abstract: Electrical Impedance Tomography Detects Peripheral Nerve Structural Changes Relevantto Diabetic Neuropathy Pooyan Pahlavan (1), Jean-Marie Bouteiller (1), Kimberly Kinga Gokoffski (2), and Gianluca Lazzi(1)(1) The University of Southern California, Los Angeles, USA (ppahlava@usc.edu)(2) The University of California, Irvine, USADiabetic neuropathy affects millions of patients worldwide and is a leading cause of sensory loss, pain, anddisability. Current diagnostic approaches primarily detect functional deficits after substantial nerve damagehas occurred, highlighting the need for methods capable of monitoring tissue-level changes during diseaseprogression. Electrical Impedance Tomography (EIT) is a non-invasive imaging technique that maps tissueconductivity and may provide a means to detect pathological changes in peripheral nerves.We investigated whether EIT can identify conductivity changes associated with peripheral nervedegeneration using computational modeling and ex vivo rat sciatic nerve experiments. Finite-elementsimulations were used to quantify EIT sensitivity to alterations in nerve conductivity representative ofstructural changes observed during neuropathic degeneration. To experimentally validate these findings,custom circumferential electrode arrays were applied to isolated rat sciatic nerves before and after inductionof ex vivo degeneration. Conductivity distributions were reconstructed from multi-electrode impedancemeasurements and compared with histological assessments of tissue structure.Both simulations and experimental measurements demonstrated detectable changes in reconstructedconductivity following nerve degeneration, and regions exhibiting altered conductivity corresponded tostructural abnormalities identified in histological sections. These results indicate that EIT is sensitive toperipheral nerve tissue changes associated with degeneration and remodeling.These findings establish EIT as a promising imaging modality for detecting structural changes in peripheralnerves and support its development as a longitudinal biomarker of neuropathy progression and therapeuticresponse.

Disclosures: P. Pahlavan: None. **J.C. Bouteiller:** None. **K.K. Gokoffski:** None. **G. Lazzi:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.22/Y32

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: C.H. Leach II Fund
NIH Grant 1R15NS140947-01A1
CDMRP Grant W81XWH-20-1-0854
NSF Grant DBI-1726368

Title: Characterizing T cell activation in the dorsal root ganglia of CCI-injured neurons

Authors: *M. A. MCQUAID[1], P. PARDEE[2], B. S. PATEL[3], J. JANJIC[4], J. A. POLLOCK[5]; [1]Biol., Duquesne Univ., Pittsburgh, PA; [2]Biol., Duquesne Univ., Latrobe, PA; [4]Pharm., [5]Dept. of Biol. Sci., [3]Duquesne Univ., Pittsburgh, PA

Abstract: Female neuroinflammation following peripheral nerve injury is thought to be driven by T cells. Specifically, T Helper (CD4+) cells and their cytokines have been identified as essential for triggering both pain and relief mechanisms following peripheral nerve injury. What has yet to be shown however, is the mechanism of T cells activation in response to nerve injury. CD4+ T cells are normally considered to be activated in germinal centers of lymph nodes by major histocompatibility class two (MHC II) complexes expressed on circulating macrophages and dendritic cells. Recently, researchers have identified MHC II protein expression in dorsal root ganglia of mice experiencing chemotherapy induced neuropathic pain associated with cold hypersensitivity1. This phenomena of MHC II expression in injured neurons of the dorsal root ganglia has yet to be shown in rats, or other nerve injury models. Here, we used chronic constriction injury (CCI) of the sciatic nerve to induce neuropathic pain. Illumina's bulk RNA-sequencing was performed on the dorsal root ganglia of sciatic nerves of CCI-injured males (n=4) and females (n=4), and their naive counterparts (n=4 per sex)2. Several MHC II subunits (RT1-Ba, RT1-Bb, RT1-Da, and RT1-Db1) were overexpressed in CCI animals. Of the CCI-injured animals, females had a greater transcript abundance of MHC II genes compared to males. Using immunohistochemistry, MHC II protein expression was identified in the plasma membrane of neuronal cell bodies within ipsilateral L4 and L5 DRGs of CCI-injured rats. We hypothesize that quantitative MHC II protein expression will reflect our transcriptomic findings, and further, that this will correspond with the local presence of T cells. These findings suggest that antigen presentation pathways are activated in DRG neurons following peripheral nerve injury and may contribute to sex-specific neuroimmune responses. References:
1 Whitaker EE et al. Expression of MHC II in DRG neurons attenuates paclitaxel-induced cold hypersensitivity in male and female mice. PLoS one. 2024;19(2):e0298396. 2. Deal B et al. RNA-Seq Reveals Sex Differences in Gene Expression during Peripheral Neuropathic Inflammation and in Pain Relief from a COX-2 Inhibiting Theranostic Nanoemulsion. Internat. J. Molec Sci. 2023;24(11):9163.

Disclosures: M.A. McQuaid: None. **P. Pardee:** None. **B.S. Patel:** None. **J. Janjic:** None. **J.A. Pollock:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.23/Z1

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH/NINDS/1UG3NS127258-01A1 UG3/UH3 (JC)
Department of Defense W81XWH-11-1-0672.10669042 (JC)
Lisa Dean Moseley Foundation (LDMF 0920JC, 1909JC, 1812JC, and 1709JC)
Cleveland Clinic Pain Management Innovations Fund #T56629 (JC)

Title: Human mesenchymal stem cells mitigated Macrophage-Mediated Neuropathic Pain

Authors: *J. ZHANG[1], J. CHENG[2];
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Abstract: Macrophage-driven neuroinflammation is a major contributor to neuropathic pain following peripheral nerve injury and represents a promising therapeutic target in chronic constriction injury (CCI). Human umbilical cord-derived mesenchymal stem cells (UCMSCs) possess potent immunomodulatory properties and may offer a non-opioid approach for limiting macrophage-mediated pain sensitization. Here, we investigated the therapeutic efficacy, donor dependence, and macrophage-targeted mechanisms of UCMSCs in a murine CCI model of persistent post-surgical neuropathic pain.UCMSCs from seven healthy donors were screened by local transplantation at the sciatic nerve ligation site immediately after CCI. Donor-dependent differences in analgesic efficacy were observed, with selected UCMSC preparations significantly improving mechanical withdrawal thresholds from day 7 onward. Local UCMSC administration attenuated mechanical allodynia and thermal hyperalgesia and improved motor performance, whereas a single intravenous injection was ineffective. CCI induced marked peripheral inflammation, characterized by increased TNF-α, IL-1β, IL-6, and CCL2 expression, infiltration of $CD45^+$ immune cells and $F4/80^+$ macrophages, and enrichment of pro-inflammatory M1 macrophages in the injured sciatic nerve. UCMSC treatment significantly reduced immune cell and macrophage infiltration, selectively suppressed M1 macrophages, and decreased spinal microglial activation, indicating coordinated inhibition of peripheral and central neuroinflammation. RNA-seq analysis further showed that UCMSCs partially reversed CCI-induced transcriptional changes and downregulated pathways associated with inflammatory signaling, neutrophil degranulation, collagen degradation, and demyelination.In vitro co-culture studies using ligated sciatic nerve tissue, sciatic nerve-derived primary cells, and LPS-stimulated Raw264.7 macrophages demonstrated direct modulation of macrophage inflammatory responses by UCMSCs. Co-culture reduced TNF-α, IL-1β, IL-6, CCL2, and iNOS expression while increasing anti-inflammatory markers Arg-1 and CD206. These effects were accompanied by robust elevation of TGF-β secretion. Collectively, these findings identify macrophages as key drivers of CCI-associated neuropathic pain and support UCMSCs as a promising non-opioid therapy that may act, in part, through TGF-β-mediated macrophage reprogramming. The results provide a mechanistic basis for further translational development of UCMSC-based interventions for neuropathic pain.

Disclosures: J. Zhang: None. **J. Cheng:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.24/Z2

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH/NINDS grant NS045594
NIH/NINDS grant NS135157

Title: Systemic administration of CGRP receptor antagonist alleviates neuropathic spontaneous pain in mice

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[1]Univ. Cincinnati Coll Med., Cincinnati, OH; [2]Anesthesiol., Univ. of Cincinnati, Cincinnati, OH; [3]Dept Anesthesiol, Col. of Med., Cincinnati, OH

Abstract: Previous work from our laboratory showed that neuropathic spontaneous pain is closely associated with mechanically evoked clustered firing of dorsal root ganglion (DRG) neurons driven by vascular movements within the DRG. Calcitonin gene-related peptide (CGRP), a potent vasodilator, is a key mediator of migraine, and CGRP receptor antagonists are highly effective for acute and preventive migraine treatment. Here, we investigated whether CGRP contributes to vasomotion-evoked neuropathic spontaneous pain in the peripheral nervous system. In the spared nerve injury (SNI) mouse model, nerve injury induced robust axonal sprouting of CGRP-positive fibers that preferentially innervated DRG blood vessels and associated pericytes. Systemic administration of the CGRP receptor antagonist BIBN 4096 (olcegepant; 1 mg/kg, i.p.) significantly reduced spontaneous pain behaviors for at least 24 h in SNI mice. Moreover, although the α1-adrenergic agonist phenylephrine (PE) typically exacerbates spontaneous pain and DRG cluster firing via vasoconstriction, BIBN 4096 pretreatment completely abolished PE-evoked spontaneous pain behaviors. To test whether CGRP itself can promote cluster firing after nerve injury, we topically applied CGRP (10 µl, 10-50 nM) to the SNI DRG. in vivo calcium imaging recording revealed that CGRP elicited only sparse, small cluster-firing events (typically 3-5 neurons per cluster) within 20 min. Together, these findings identify CGRP signaling as a critical contributor to spontaneous pain after peripheral nerve injury and support further mechanistic studies. Clinically approved CGRP receptor antagonists (gepants; e.g., rimegepant, atogepant, ubrogepant, zavegepant) may therefore represent a promising therapeutic strategy for peripheral nerve injury-induced spontaneous pain.

Disclosures: W. Xie: None. **T. Berta:** None. **J. Zhang:** None.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.25/Z3

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Mechanoelectric changes in dorsal root ganglia neurons 24 hours after spinal cord injury and implications for neuropathic pain

Authors: *C. ADAM[1], R. STINGEL[2], J. CRODIAN[4], R. SHI[3];
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Abstract: Spinal cord injury (SCI) affects millions worldwide. Chronic pain after SCI is often rated as one of the most detrimental side effects, even compared to motor deficits, arises from overactive pain signaling to the brain, and is difficult to manage or reverse clinically without greater mechanistic understanding. Key cells involved in producing neuropathic pain are neurons in the dorsal root ganglia (DRG), which bridge the spinal cord and peripheral nervous system. While the initial SCI damage (primary injury) mostly affects the spinal cord, additional biochemical damage (secondary injury) spreads to the DRG within 24 hours of the primary injury and can persist for years. Chronic secondary injury renders DRG cells hypersensitive and hyperactive, increasing pain signals that contribute substantially to neuropathic pain. However, greater understanding of the sensitization process, especially at acute timepoints after injury, is needed to design effective pain management strategies. In particular, how physical and chemical damage alter DRG electrical signaling is unclear. Previous work has primarily evaluated the biochemical and electrical properties of DRG neurons after SCI. However, the chemical, electrical, mechanical, and magnetic properties of neurons and action potentials are coupled, meaning that changes in any of these properties influence all others. Therefore, measuring and comparing multiple cell properties instead of solely electrical or biochemical properties can provide more insight into cell function. As “how things move determines how things function,” mechanical properties are ideal for comparison against cell electrophysiology. Additionally, mechanical properties have been shown to influence neuronal firing and better understanding and quantification of the link between cell mechanics, electrophysiology, and function could therefore provide greater insight into the cellular effects of SCI. This work measured and quantified the mechanical and electrical properties of individual DRG neurons isolated from male Sprague-Dawley rats 24 hours after the animal was subject to SCI, sham injury, or no injury. Atomic force microscopy (AFM) was used to measure mechanical properties, and whole cell patch clamp was used to measure electrical properties. SCI altered both the mechanical properties, specifically viscoelasticity, and the electrical properties of DRG neurons. By revealing how both cell mechanics and electrophysiology change shortly after SCI, these experiments provide a useful platform to understand the initial changes that eventually lead to chronic pain and hypothesize novel therapeutic avenues.

Disclosures: C. Adam: None. **R. Stingel:** None. **J. Crodian:** None. **R. Shi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurovigor.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.26/Z4

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: SIR2501, a novel SARM1 Inhibitor, Demonstrates Favorable Safety, Predictable Pharmacokinetics, and Early Signals of Protection Against Chemotherapy-Induced Peripheral Neuropathy

Authors: ***S. AGARWAL**[1], L. SONG[2], B. WANG[2], S. WU[2], D. GRACHEV[1], J. QIU[2], V. LATIFI[3], A. RAJARETHINAM[1], W. FAN[2];
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting toxicity of taxane chemotherapy, with no approved therapies for prevention or treatment. Activation of the neuronal NAD^+ hydrolase SARM1 drives rapid NAD^+ depletion and axonal energy failure, a mechanism strongly implicated in CIPN pathogenesis; genetic and pharmacologic SARM1 inhibition prevents axonal degeneration in multiple CIPN-relevant models. SIR2501 is a novel, allosteric, brain-penetrant SARM1 inhibitor in clinical development for CIPN prevention and mitigation. We first evaluated the safety, pharmacokinetics (PK), and pharmacodynamic profile of SIR2501 in a randomized, double-blind, placebo-controlled first-in-human study in healthy adults (n=88) and we are currently assessing its safety and preliminary clinical activity in CIPN. In healthy participants, SIR2501 was well tolerated, with no serious adverse events, no Grade ≥3 treatment-emergent adverse events, and only mild to moderate asymptomatic laboratory abnormalities deemed unrelated to study drug. SIR2501 demonstrated rapid absorption, a prolonged elimination half-life, moderate accumulation, and linear, time-independent PK, supporting once-daily dosing. We are currently evaluating its safety, pharmacokinetics (PK), and early activity in patients with solid tumor receiving paclitaxel-based chemotherapy. In an ongoing global Phase 1b/ 2 open-label CIPN study, eighteen patients have been treated at multiple dose levels (30 mg [n=6], 45 mg [n=6], 60 mg [n-6]). Safety data are reviewed by an independent Safety Review Committee at prespecified intervals. Assessments included blood neurofilament light chain (NfL), EORTC QLQ-CIPN20 sensory scores, Total Neuropathy Score (TNS/TNSc), and NCI-CTCAE grading. Across completed cohorts, SIR2501 has been well tolerated, with no dose-limiting toxicities, one not related serious adverse event, and no clinically meaningful abnormalities in vital signs, laboratory parameters, or ECGs; all adverse events to date have been assessed as unrelated to study drug. Additionally, there were no reported dose modifications due to an adverse event of neuropathy. The preliminary results support the safety and PK suitability of SIR2501 for use alongside paclitaxel and provide preliminary evidence which is consistent with SARM1 pathway engagement. Collectively, the results suggest continued development of SIR2501 as a first-in-class therapeutic candidate for prevention and mitigation of chemotherapy-induced peripheral neuropathy.

Disclosures: S. Agarwal: A. Employment/Salary (full or part-time):; SIRONAX. **L. Song:** A. Employment/Salary (full or part-time):; SIRONAX. **B. Wang:** A. Employment/Salary (full or part-time):; SIRONAX. **S. Wu:** A. Employment/Salary (full or part-time):; SIRONAX. **D.**

Grachev: 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.; SIRONAX. **J. Qiu:** A. Employment/Salary (full or part-time):; SIRONAX. **V. Latifi:** A. Employment/Salary (full or part-time):; SIRONAX. **A. Rajarethinam:** A. Employment/Salary (full or part-time):; SIRONAX. **W. Fan:** A. Employment/Salary (full or part-time):; SIRONAX.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.27/Z5

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Targeted Immunomodulation via Plasmapheresis Reverses Small Fiber Degradation and Alleviates Widespread Pain in a Fibromyalgia-CIDP Overlap Spectrum: A Clinical and Reverse Translational PET/CT Study

Authors: *N. PRAKASH[1], X. CARO[2], J. SHIVELY[3];
[1]City of Hope Natl. Med. Ctr., Duarte, CA; [2]Southern California Fibromyalgia Res. & Treatment Ctr., Northridge, CA; [3]City of Hope, Duarte, CA

Abstract: Introduction: Fibromyalgia (FM) widespread pain has historically been classified as centrally mediated. However, a significant overlap exists with peripheral neuroinflammatory pathologies; on the order of 50% of FM patients exhibit small-fiber neuropathy (SFN), and a subset satisfy electrodiagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). We hypothesized that circulating immune mediators drive peripheral nerve injury and small-fiber degradation, making immunomodulation via plasmapheresis (PLEX) a viable intervention. To clarify the systemic behavior of these circulating factors, we paired our clinical findings with a reverse translational animal model tracking patient-derived IgG. Methods: Clinical: Eight subjects meeting ACR criteria for FM resistant to standard therapies and with electrodiagnostic features of any CIDP variant underwent 5 PLEX sessions over 5-8 days. Outcomes included subjective quality of life (QOL), Tender Point Count (TPC), Fibromyalgia Impact Questionnaire-Revised (FIQ-R), and thigh and calf 3 mm punch skin biopsy for Epidermal Nerve Fiber Density (ENFD). Translational: IgG purified from FM patient plasma or healthy control IVIG was administered to C57Bl/6 mice. Whole-body micro-PET/CT imaging was conducted at 4h, 24h, and 48h to quantify clearance rates and anatomical sequestration. Results: Clinical: All participants reported striking subjective improvements in QOL, neuropathic symptoms, and "brain fog" post-PLEX. Subjects demonstrated a mean increase of 2.5 fibers/mm in ENFD, alongside significant improvements of 23 points in FIQ-R and 6.38 in TPC. At least one autoantibody (most commonly ANA) was present in 75% of participants. Translational: PET/CT revealed a significantly accelerated blood tracer clearance rate and increased, diffuse whole-body tracer uptake in FM IgG-treated mice compared to IVIG controls. This widespread tissue sequestration was verified via localized FM

IgG uptake in hind paw skin small nerve fibers and spinal dorsal root ganglion. Conclusions: These findings demonstrate that PLEX is safe, well-tolerated, and objectively reverses peripheral small fiber degradation while mitigating clinical pain severity. The rapid clearance and diffuse systemic tissue accumulation of FM IgG in vivo suggest a global, pathogenic antibody-tissue interaction that extends far beyond localized neural structures, validating an autoimmune etiology for a distinct subset of FM patients.

Disclosures: N. Prakash: A. Employment/Salary (full or part-time):; City of Hope, Clinical Professor, Chief of Neurology. **X. Caro:** None. **J. Shively:** A. Employment/Salary (full or part-time):; City of Hope, Department of Immunology & Theranostics.

Poster

PSTR357: Peripheral Nerve Damage, Neuropathic Pain, and Repair

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.28/Z6

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: DoD Grant W81XWH-18-1-0321
DoD Grant W81XWH-20-1-0802
VA Merit Review 5 I01 RX003566-02
NIH Training Grant T32EB004314

Title: Towards Improving Tissue Health in the Lower Limb via Sensory Nerve Stimulation

Authors: *H. S. MORGAN[1,2], R. J. TRIOLO[1,2], H. CHARKHKAR[1,3];
[1]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [2]Advanced Platform Technol. Ctr., Louis Stokes Cleveland Dept. of Veteran Affairs Med. Ctr., Cleveland, OH; [3]Advanced Platform Technol. Ctr., Louis Stokes Cleveland Med. Ctr., Cleveland, OH

Abstract: Skin breakdown in the extremities is a highly debilitating complication impacting around 50% of adults with diabetes and 66% of individuals with lower limb loss. Minor insults to the tissue can progress to widespread infection that necessitates surgical intervention. In addition to the direct effects on the tissue, skin breakdown in the lower limb can limit mobility and reduce independence, driving sedentary behavior and social isolation. Protective peripheral neurovascular mechanisms have been shown to be disrupted in these populations, leaving the skin of the lower limb highly vulnerable. We have previously demonstrated that reflexive vasodilation in response to heating is attenuated in areas with loss of cutaneous sensation in individuals with diabetic peripheral neuropathy. These protective reflexes directly rely on the activity of sensory nerves to rapidly adjust skin blood flow to minimize injury when tissue is exposed to stress. Therefore, it was hypothesized that electrical stimulation of sensory afferents in the lower limb has the potential to modulate the magnitude of reflexive vasodilation responses. In this study, we quantified the effect of sensory nerve stimulation in the lower limb on reflexive vasodilation in individuals with lower-limb loss. Perfusion was measured using laser

Doppler flowmetry during non-noxious local heating. The amplitude of the neurogenic peak phase and the area under the curve were quantified in the skin of the residual limb during stimulation of the residual sciatic or tibial nerves using chronically implanted extraneural cuff electrodes in three individuals with traumatic lower limb loss. Stimulation parameters were selected to elicit percepts in the missing foot at a comfortable intensity for each participant. Percept locations, intensities, and modalities were collected in order to analyze correlations between percept characteristics and vasodilation response outcome metrics. Sensory nerve stimulation significantly increased the median neurogenic peak amplitude and the area under the curve ($p < 0.01$) relative to the no stimulation control condition. A 20% reduction in variability of the neurogenic peak amplitude was also observed. These results indicate that sensory nerve stimulation has the potential to modulate reflexive vasodilation. These findings have important implications for developing interventions to improve peripheral neurovascular responsiveness and increase the robustness of protective mechanisms in the skin in vulnerable populations. Future work includes collection of additional data in individuals with limb loss and investigation of non-invasive stimulation modalities.

Disclosures: H.S. Morgan: None. **R.J. Triolo:** None. **H. Charkhkar:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.01/Z7

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: iPSC-derived mesenchymal stem cell neural progenitors (iMSC-NPs) from multiple sclerosis donors attenuate microglial and T cell activation in vitro

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Abstract: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by chronic demyelination, microglial activation, reactive astrogliosis, and axonal loss, leading to progressive neurologic decline. Because therapeutic options for progressive MS remain limited, mesenchymal stem cell (MSC)-based therapies have been investigated for their immunoregulatory and neuroprotective effects. We have investigated the therapeutic efficacy of bone marrow-derived MSC neural progenitor-like cells (MSC-NPs), which exhibit enhanced expression of neural and signaling-related genes and can modulate both T cell and microglial activity. However, clinical studies using autologous intrathecal MSC-NPs have produced inconsistent outcomes, likely due to donor-dependent variability in adult bone marrow-derived cell populations. As an alternative autologous cell source with improved tissue-repair capacity, we developed iMSC-NP populations from induced pluripotent stem cells (iPSCs). Differentiation of iPSCs into MSCs (iMSCs) was achieved through inhibition of

GSK3β and TGFβ for one week, followed by expansion in MSC growth media. After five passages, iMSCs exhibited key phenotypic properties of bone marrow-derived MSCs, including expression of characteristic cell surface markers and adipogenic and osteogenic differentiation capacity. To evaluate the functional capacity of iMSCs to modulate microglia and T cell activity in vitro, stimulated C20 and iPSC-derived microglia were cultured in conditioned media from iMSCs and iMSC-NPs. RNA was collected for PCR analysis, and Luminex assays were performed to assess changes in CCL2, CCL5, CCL8, and IL-6 expression. In parallel, PBMCs were cocultured with varying densities of iMSCs. T cell activation and proliferation was analyzed by flow cytometry, and release of IFN-γ, IL-10, IL-2, and TNF-α analyzed by Luminex assay. In both experiments, reduction of cytokine and chemokine expression was consistent between MSC and iMSC groups. Results were comparable using iMSCs generated from healthy control, secondary progressive MS and primary progressive MS donors. These results suggest the functional equivalence of iPSC-derived iMSC to bone marrow derived MSCs and support their being used for regenerative cell therapy in progressive MS.

Disclosures: S. Ricciarini: None. **V.K. Harris:** None. **S.A. Sadiq:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.02/Z8

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: JSPS KAKENHI 25K10752
JSPS KAKENHI 25K10729
Takeda Science Foundation 2400341

Title: Primary Cilia Elongation Is Associated With Neuroprotection in Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis

Authors: *R. ODA[1], N. IWAHARA[1], T. NONAKA[1], M. TANEMOTO[1], M. YAMAMOTO[1], A. KUNO[2], S. HISAHARA[1];
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Abstract: Neurodegeneration, which begins early in the disease course, is increasingly recognized as a major contributor to disability in multiple sclerosis (MS). Reanalysis of our previously published proteomic dataset of cerebrospinal fluid-derived extracellular vesicles (EVs) from patients with MS (Neurol Neuroimmunol Neuroinflamm. 2025;12(5):e200442) and publicly available single-nucleus RNA sequencing (snRNA-seq) data from postmortem human brains revealed alterations in primary cilia-related molecules, suggesting a potential role for

primary cilia in MS pathology. Primary cilia are organelles that serve as hubs for multiple signaling pathways and dynamically change their length in response to cellular and environmental conditions. To investigate the relationship between primary cilia and neurodegeneration, we utilized experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. EAE was induced by immunization with myelin oligodendrocyte glycoprotein $(MOG)_{35-55}$ peptide (n=20). During the chronic phase (84-90 days post-immunization), mice underwent Y-maze testing, brain MRI, western blotting, and spinal cord immunofluorescence analyses. Chronic EAE mice exhibited cognitive impairment, brain atrophy, and a reduced number of spinal motor neurons, indicating neurodegeneration. Primary cilia in spinal motor neurons were visualized by immunostaining with an anti-adenylate cyclase III (AC3) antibody and were significantly elongated in EAE mice ($n = 5$, $p < 0.001$). Moreover, ciliary length showed a strong positive correlation with the number of surviving motor neurons ($n = 7$, $r = 0.94$, $p = 0.001$). To model acute spinal inflammation, lipopolysaccharide (LPS) derived from Escherichia coli was administered intrathecally, which also resulted in elongation of neuronal primary cilia ($n = 4$, $p < 0.001$). In vitro, SH-SY5Y cells were transfected with siRNAs targeting the primary ciliary proteins IFT88 and KIF3A to induce ciliary dysfunction. Knockdown of either IFT88 or KIF3A reduced cell viability under H_2O_2-induced oxidative stress ($n=4$, $p < 0.05$), whereas activation of Sonic Hedgehog (SHH) signaling by smoothened agonist (SAG) improved cell viability ($n=4$, $p < 0.05$). These findings suggest that primary cilia are involved in MS pathology and may exert neuroprotective effects in response to neuroinflammation. Furthermore, primary cilia and SHH signaling appear to contribute to neuronal survival, highlighting primary cilia as a potential therapeutic target for neurodegeneration in MS.

Disclosures: R. Oda: None. **N. Iwahara:** None. **T. Nonaka:** None. **M. Tanemoto:** None. **M. Yamamoto:** None. **A. Kuno:** None. **S. Hisahara:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.03/Z9

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: FISM 2024/BR/007

Title: Modeling Progression Independent of Relapse Activity with a Transgenic Model of Demyelination Induced by Oligodendrocyte-specific Mitochondrial DNA damage

Authors: *A. MINI[1], M. J. PLASTINI[1], E. JUAREZ[1], A. BRAKE[1], C. MORAES[2], K. L. LAMBERTSEN[3,4], C. LANGSETH[5], L. KIRBY[5], G. CASTELO-BRANCO[5], R. BRAMBILLA[1,4];
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Abstract: Multiple Sclerosis (MS) has traditionally been classified into relapsing remitting and progressive forms, with relapsing MS transitioning into progressive overtime. However, recent evidence indicates progression starts at disease onset even in the absence of relapses, a phenomenon defined *progression independent of relapse activity* (PIRA). The mechanisms driving PIRA are poorly understood, partly due to lack of animal models that capture its key pathological features. To address this need, we developed the PLP:mtPstI mouse model of demyelination, where timed expression of the endonuclease PstI in mitochondria (mt) of myelinating OLs causes progressive mtDNA damage. Overtime, this leads to OL cell death, axonal damage and demyelination accompanied by sensory-motor deficits, recapitulating hallmarks of PIRA. Since our objective is to leverage the PLP:mtPstI model to understand the mechanisms driving PIRA, we analyzed mice at various times after induction of OL-specific mtDNA damage. We observed impairment of motor coordination at 4 months, with further deterioration at 6 months indicating progressive neurodegeneration. Consistent with this, serum concentrations of NfL, GFAP and Tau were significantly elevated starting at 4 months. Affected mice displayed lower body weight already at 2 months, when demyelination is minimal, suggesting broader systemic effects due to disease progression. Moreover, we observed that demyelination was accompanied by limited immune cell infiltration in the brain. Immune cells formed subpial-like clusters containing lymphocytes and myeloid cells, resembling subpial lymphoid structures seen in PIRA. By flow cytometry, we found B cells to be the population with the earliest significant increase (between 2 and 4 months), while CD4 and CD8 T cells were elevated at later times (6 months). Interestingly, we detected a population of OLs expressing MHCII, suggesting an emerging immune phenotype. To assess abundance, distribution and cell-cell interactions of distinct populations, we employed spatial transcriptomics where, in preliminary analyses, we identified a population of disease-associated OLs with elevated expression of Serpina3n in PLP:mtPstI mice 2 months after induction of mtDNA damage. Together our findings indicate the PLP:mtPstI model recapitulates key features of MS progression, representing a valuable tool to investigate the mechanisms of PIRA and identify new therapeutic targets to address MS progression.

Disclosures: A. Mini: None. **M.J. Plastini:** None. **E. Juarez:** None. **A. Brake:** None. **C. Moraes:** None. **K.L. Lambertsen:** None. **C. Langseth:** None. **L. Kirby:** None. **G. Castelo-Branco:** None. **R. Brambilla:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.05/Z11

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Role of ISG15 in neuronal homeostasis

Authors: *G. MORALES[1], B. CLARKSON[2];
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Abstract: Background: ISG15 is induced in neurons by demyelination and elevated in MS patient cortical neurons. We hypothesize that ISG15 contributes to neuron loss in MS by impairing ubiquitin-dependent protein degradation pathways and mitochondrial turnover.**Methods**: **In vivo:** C57BL/6 wild-type (WT) and ISG15 knockout (KO) mice were subjected to a cuprizone-induced demyelination. Neuronal density changes in the cortex were assessed longitudinally using immunofluorescence staining and confocal microscopy. **In vitro:** ISG15 expression was induced in cortical neurons by treatment with interferon-γ (IFNγ). **Autophagy:** Cortical neurons were transduced with AAV.CLEAR.mKeima.eGFP.LC3B to assess activation of the lysosomal-autophagy transcriptional program and autophagic flux. This reporter utilizes the CLEAR (Coordinated Lysosomal Expression and Regulation) promoter, a TFEB/TFE3- responsive regulatory element that drives expression of genes involved in autophagy. In this system, eGFP signal reflects activation of the TFEB/TFE3- dependent CLEAR network, while mKeima fluorescence serves as an indicator of autophagic flux. In addition, cortical neurons were transduced with AAV1.SYN1.mKeima.eGFP.LC3B to monitor autophagic flux. This reporter enables visualization of LC3B trafficking through the autophagy pathway. Total eGFP signal was used as a measure of autophagosome abundance, while mKeima signal served as an indicator autophagic flux. **Mitophagy:** Cortical neurons were transduced with AAV.SYN.mt-mKeima.eGFP.FIS1, a neuron-specific mitophagy reporter that targets mitochondria via FIS1. During mitophagy, eGFP fluorescence is quenched following delivery of mitochondria to acidic lysosomes, while mt-mKeima remains stable and fluorescent. The mt-mKeima signal therefore identifies mitochondria within lysosomes and enables quantification of mitophagic flux.**Results**: Neuron density was preserved in ISG15 KO compared to control. Using the CLEAR promoter, ISG15- deficient cortical neurons exhibited reduced activation of the TFEB/TFE3- dependent autophagy transcriptional program. Relative to WT controls, ISG15-deficient neurons showed altered autophagy and mitophagy reporter dynamics following IFNγ treatment and showed elevated mitochondrial content.**Conclusion**: IFNγ-induced ISG15 impairs autophagy and mitochondrial turnover in neurons, and ISG15 deficiency protects neurons during demyelinating disease. Future work will test neuron-specific condition ISG15 ablation and determine how ISG15 impacts mitochondrial health and cell death pathways in neurons during neurodegeneration.

Disclosures: G. Morales: None. **B. Clarkson:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.06/Z12

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NINDS-R01NS117533
NINDS-F32NS134683
AMRF-Adelson Medical Research Foundation

Title: Neuronal subtype vulnerability to microglial-induced synapse loss in demyelinating disease

Authors: *C.-W. CHEN[1,2], R. XIAO[1,2], R. BEITER[1], A. BATTISON[3], J. C. BORNIGER[3], D. P. SCHAFER[1,2];
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Abstract: Synapse loss is a well-known pathological hallmark of neurodegenerative diseases and has been directly linked to clinical symptoms. More recent work has also established that synapse loss can be observed in numerous brain regions in patients with multiple sclerosis (MS), a demyelinating disease of central nervous system (CNS) that affects over 2 million people worldwide. Importantly, current work indicates that synapse loss may be an acute driver of clinical deterioration, independent of active demyelination. Work in animal models of MS has demonstrated that synapse loss is driven by deposition of the complement component C3 and subsequent synaptic engulfment by microglia. However, it remains unclear why some synapses are targeted for removal over others, and what mechanisms cause these synapses to be more vulnerable or resilient to loss. We use the retinogeniculate circuit to assess changes in retinal ganglion cells (RGCs) synapses in the brain and cell body in the retina. Using the experimental autoimmune encephalomyelitis (EAE), a mouse model relevant to MS, we found that a subtype of RGCs, called αRGCs, are lost at a significantly higher rate than non-αRGC synapses. Surprisingly, we saw the opposite effect in cell body loss, with non-αRGC cell bodies being lost at a higher rate than αRGC cell bodies. In both αRGC and non- αRGCs, synapse loss preceded any observation of cell body loss. To understand the potential molecular mechanisms regulating synaptic vulnerability, we are using an antibody-based proximity labeling approach and mass spectrometry to characterize the synaptic proteome in specific subsets of RGCs during EAE. The initial proteomic results suggest that antioxidant enzymes are downregulated specifically in αRGC synapses during EAE, providing a potential mechanism for their enhanced vulnerability to synapse loss. Taking together, our work demonstrates that specific subtypes of neurons are more vulnerable to microglial-induced synapse loss in neurodegenerative disease. This work provides a deeper understanding of how neuronal identity drives synapse loss in neurodegenerative disease and lays the groundwork for future investigation into the mechanisms that drive this selective synaptic vulnerability.

Disclosures: C. Chen: None. **R. Xiao:** None. **R. Beiter:** None. **A. Battison:** None. **J.C. Borniger:** None. **D.P. Schafer:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.07/Z13

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: National Institute of Neurological Disorders and Stroke (NINDS) R35NS111644
Valhalla Foundation
Westridge Foundation

Title: A neurotoxic B-cell secretome in multiple sclerosis

Authors: *C. SAHA[1], K. LENG[1], M. JACKSON[1], A. ZHANG[1], J. MCKETNEY[1], M. KARALIUS[1], M. LOUINE[2], C. GERUNGAN[1], R. GOMEZ[1], M. HARMS[3], A. TUBATI[1], T. COOPER[1], D. SWANEY[1], N. J. KROGAN[1], E. M. ULLIAN[1], J. SABATINO[1], J. OKSENBERG[1], B. CREE[1], M. KAMPMANN[1], M. R. WILSON[1], S. L. HAUSER[1];
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Abstract: In multiple sclerosis (MS), B-cell-rich lymphoid aggregates form in deep meninges adjacent to cerebral sulci and in perivascular spaces of the CNS, where they contribute to cortical neurodegeneration, demyelination, and clinical progression. Little is known, however, about exactly how these B-cells contribute to MS pathology. Here, we assessed the effects of secreted factors from human B-cells on neuronal viability in vitro. $CD19^+$ B-cells were isolated from peripheral blood of treatment-naïve MS patients and age/sex matched healthy controls (HC), and cultured as unstimulated (UNS), or following stimulation with anti-IgM/G/A and CD40L with or without CpG. After 3 days, the B-cell media (BCM) were added to human induced pluripotent stem cell (iPSC)-derived day 14 glutamatergic neurons (i3N). Neurotoxicity was quantified by thiazole red staining. Size fractionation, Ig depletion, and blocking experiments were performed to identify factors responsible for B-cell-mediated toxicity. RNA-seq and mass spectrometry were used to profile B-cell and i3N transcriptomic and proteomic responses. We report that UNS-BCM were consistently neurotoxic to i3N. In MS subjects, neurotoxicity was higher than in paired HCs, overall (31.7% vs. 24.3%; mean difference 7.3 percentage points, adjusted *p=0.0027*). Pairwise analysis revealed significantly greater neurotoxicity in 9 of 24 matched MS-HC pairs (37.5%). This was primarily present in the low-molecular-weight (<30 kDa) fraction, while absent from Ig-containing and high-molecular-weight (including exosome) fractions. Neurotoxicity was associated with elevated levels of proinflammatory molecules secreted by B-cells, including TNF-α, IL-8, RANTES, MDC, and MIP-1β, and could be partially blocked by neutralizing TNF-α or TNFR1 (HC $P < 0.0001$; MS $P < 0.01$). Neuronal transcriptomic responses to B-cell secretome exposure were characterized by coordinated suppression of synaptic and cholesterol pathways, which intensified with increasing toxicity. Additionally, proteomic analysis revealed decreased levels of BCL-2 protein in i3neurons treated with MS B-cell supernatants, indicating disruption of survival signals. Finally, MS B-cell proteomic profiling revealed that levels of BAFF were reduced by approximately two-fold (*MSstats p=0.00037*) compared with HC, supporting a model in which low BAFF availability or impaired BAFF signaling skews B-cells toward excessive TNF-α production. Taken together, these data

define molecular characteristics of the B-cell secretome responsible for neurotoxicity and suggest novel neuroprotective strategies against immune-mediated neurodegeneration.

Disclosures: C. Saha: None. **K. Leng:** None. **M. Jackson:** None. **A. Zhang:** None. **J. McKetney:** None. **M. Karalius:** None. **M. Louine:** None. **C. Gerungan:** None. **R. Gomez:** None. **M. Harms:** None. **A. Tubati:** None. **T. Cooper:** None. **D. Swaney:** None. **N.J. Krogan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GEn1E Lifesciences, Maze Therapeutics, Rezo Therapeutics, Tenaya Therapeutics. F. Consulting Fees (e.g., advisory boards); GEn1E Lifesciences, Tenaya Therapeutics, Maze Therapeutics, Rezo Therapeutics. **E.M. Ullian:** None. **J. Sabatino:** 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.; Novartis, Roche/Genentech. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Roche/Genentech, IgM Biosciences, TG Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sift Biosciences. **J. Oksenberg:** None. **B. Cree:** None. **M. Kampmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Montara Therapeutics. F. Consulting Fees (e.g., advisory boards); Montara Therapeutics, Engine Biosciences, Alector, Modulo Bio, Theseus Therapies. **M.R. Wilson:** 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.; Kyverna Therapeutics, Novartis, Roche/Genentech. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Delve Bio, Inc. F. Consulting Fees (e.g., advisory boards); Pfizer, Vertex Pharmaceuticals, Ouro Medicines, Indapta Therapeutics, Delve Bio, Inc. **S.L. Hauser:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alector, Neurona. F. Consulting Fees (e.g., advisory boards); Accure, Alector, Hinge Bio, Neurona. Other; Hoffmann-La Roche, Novartis AG.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.08/Z14

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: AMED 25be1004103h0001

Title: Reconstruction and Electrophysiological Characterization of Human iPSC-derived Saltatory Conduction Models on Ultra-High-Density CMOS Microelectrode Arrays

Authors: *B. NODA, X. HAN, M. YAMANAKA, N. MATSUDA, I. SUZUKI;
Tohoku Inst. of Technol., Sendai, Japan

Abstract: Background: Saltatory conduction via myelinated axons enables rapid signal transmission in the human peripheral nervous system. Although rodent models are widely used, species differences limit their translation to human pathophysiology. Reconstituting a functional human myelination model in vitro remains challenging due to complex sensory neuron (SN) and Schwann cell (SC) interactions. Here, we established a human in vitro co-culture system to model saltatory conduction and evaluated its morphological and electrophysiological properties.
Methods: Human induced pluripotent stem cells (iPSCs) were differentiated into functional SNs and mature SCs. To assess myelination, cells were co-cultured on ultra-high-density CMOS microelectrode arrays (UHD-CMOS-MEA) for label-free, high-resolution recording of extracellular action potentials along single axons. Structural maturation was characterized using scanning electron microscopy (SEM) and immunocytochemistry for myelin basic protein (MBP) and β-III-tubulin (Tubb3).
Results: Morphological analyses demonstrated successful myelin formation. SEM imaging revealed wrapped, multi-layered myelin structures surrounding SN axons. Immunofluorescence confirmed that MBP signals were longitudinally aligned along Tubb3-positive axons, indicating targeted myelination by iPSC-derived SCs. Crucially, UHD-CMOS-MEA recordings demonstrated functional maturation of signal propagation. Co-culturing with SCs significantly increased axonal conduction velocity compared to SN-only cultures. Furthermore, high-density tracking of action potentials revealed non-linear, discrete propagation patterns with microsecond resolution, strongly indicating saltatory conduction along myelinated segments.
Conclusion: We developed a human iPSC-derived platform recapitulating structural and electrophysiological features of myelination and saltatory conduction. Integrating iPSC technology with UHD-CMOS-MEA provides a powerful, quantitative tool to track signal velocity at the single-axon level. This platform opens new avenues for modeling human demyelinating diseases, such as Charcot-Marie-Tooth disease, and serves as a scalable tool for screening myelin-regenerating therapeutics.

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Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.09/Z15

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: PIFF25-1 UAA
SECIHTI-908627
SECIHTI-616297

Title: Blocking Vasopressin V1a and V2 receptors attenuates clinical progression and Th1/Th17-related gene expression in a rat model of experimental autoimmune encephalomyelitis

Authors: *F. VALDEZ URIAS[1], A. CALVILLO-ROBLEDO[1], I. MARTÍNEZ VALERIANO[1], M. E. ESPARZA MARTINEZ[1], A. QUINTANAR STEPHANO[2];
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Abstract: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by immune cell infiltration, demyelination, and progressive axonal damage. Arginine vasopressin (AVP), in addition to its endocrine role in fluid balance, has been increasingly implicated in immune regulation and neuroinflammatory responses. This study aimed to determine whether pharmacological blockade of AVP receptors with conivaptan (CNV), a dual V1a/V2 receptor antagonist, modulates clinical and molecular progression in chronic experimental autoimmune encephalomyelitis (EAE), an established model of MS. Female Lewis rats were immunized with guinea pig brain extract emulsified in Freund's complete adjuvant to induce EAE, except in the intact control group. CNV was administered to the corresponding treatment groups during the early inflammatory phase (day 9) or after the onset of neurological signs (day 18). Clinical evolution was monitored for 30 days. Serum copeptin was quantified by ELISA as an indirect marker of AVP activity, and the expression of Th17- and Th1-related inflammatory genes in the spinal cord and spleen was assessed by RT-qPCR. Serum copeptin levels correlated positively with the clinical severity of EAE, supporting an association between AVP signaling and neuroinflammatory disease activity. Animals treated with CNV showed reduced clinical scores compared to untreated EAE rats, indicating an attenuation of neurological deterioration. At the molecular level, CNV decreased the expression of RORγt and IL-17A, key mediators of Th17 differentiation and activity, in both the spinal cord and spleen, and reduced IFN-γ expression in the spinal cord, suggesting broader downregulation of proinflammatory immune pathways. These findings indicate that AVP receptor blockade can limit autoimmune neuroinflammation by suppressing Th17-associated responses in the spinal cord and spleen and reducing the Th1 response in the spinal cord. In conclusion, CNV attenuated the progression of EAE and could represent a promising pharmacological strategy for modulating neuroimmune interactions relevant to MS. Further studies are needed to define its therapeutic window, long-term safety, and translational potential in autoimmune demyelinating diseases.

Disclosures: F. Valdez Urias: None. **A. Calvillo-Robledo:** None. **I. Martínez Valeriano:** None. **M.E. Esparza Martinez:** None. **A. Quintanar Stephano:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

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Program #/Poster #: PSTR358.10/Z16

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: PIFF25-1UAA
SECIHTI616297
SECIHTI908627

Title: Pharmacological blockade of vasopressin receptors: Correlation between V1a signaling and disease severity in a re-immunized EAE Model

Authors: *A. CALVILLO-ROBLEDO[1], F. VALDEZ URIAS[1], A. QUINTANAR STEPHANO[2], B. GUTIERREZ[1];
[1]Fisiología y Farmacología, Univ. Autónoma de Aguascalientes, Aguascalientes, Mexico;
[2]Fisiología y Farmacología, Univ. Autónoma de Aguascalientes, Aguascalentes, Mexico

Abstract: Multiple sclerosis (MS) is a chronic neuroinflammatory disease characterized by progressive demyelination of the central nervous system. In this condition, activated immune cells cross the blood-brain barrier and initiate an inflammatory response against myelin antigens, leading to neurological impairment including motor dysfunction, sensory disturbances, and cognitive decline. Experimental autoimmune encephalomyelitis (EAE) is a widely used model that recapitulates key clinical and pathological features of relapsing-remitting MS. Previous studies have shown that arginine vasopressin (AVP) deficiency, as well as pharmacological blockade of its V1a and V2 receptors, ameliorates clinical and histopathological outcomes in acute EAE models. In the present study, we evaluated, in a chronic EAE model with re-immunization, the expression of V1a and V2 receptors, their association with disease severity, and the profile of Th17 and regulatory T cells following treatment with conivaptan. Our results demonstrate that the re-immunized EAE model successfully reproduces relapse-remission dynamics characteristic of MS. Histopathological analysis revealed reduced lymphocytic infiltration in the conivaptan-treated group. Furthermore, V1a expression showed a significant positive correlation with clinical severity, whereas no significant changes were observed in Th17 and Treg populations. These findings suggest that modulation of the vasopressinergic axis, particularly through V1a signaling, may contribute to disease progression independently of major quantitative changes in peripheral immune cell subsets.

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Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.11/Z17

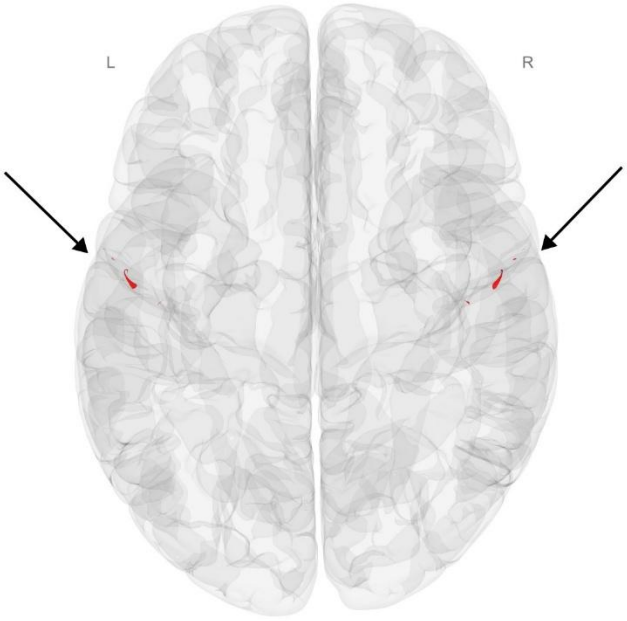
Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan Grant No. BR27198099

Title: Sensorimotor Fucntional Connectivity Reorganization Driven by Lesion Burden in Relapsing-Remitting Multiple Sclerosis

Authors: *D. KALMAGAMBETOV[1], M. MELNIKOV[2], G. MATTHEWS[4], A. KUSTUBAYEVA[3];
[1]Brain Institute, Farabi Univ., Almaty, Kazakhstan; [3]Dept. of Biophysics, Biomedicine, and Neurosci., [2]Farabi Univ., Almaty, Kazakhstan; [4]George Mason Univ., Washington, DC

Abstract: Multiple sclerosis (MS) induces structural damage to white matter pathways that may disrupt normal functional connectivity pattern though often triggers compensatory functional reorganization within motor circuits. Given probable comissural fibers involvement, interhemispheric connectivity may suffer greatest damage and require largest functional restoration. To clarify the relationships between white matter dysruption and functional connectibity rewiring, we investigated how lesion burden influences inter-hemispheric functional connectivity in patients with relapsing-remitting MS. Eighteen patients with relapsing-remitting MS (15 women, 3 men; mean age ± SD: 34.4 ± 10.6 years) were recruited. Imaging data were collected using a 3T GE SIGNA Architect scanner, including T1-weighted structural images, T2 FLAIRs, and 10-minute (200 volumes) resting-state functional data. The hyperintensity lesions were identified and segmented from T2 FLAIR images using the LST 3 toolbox, and fMRI data were processed in the Conn 22 toolbox. The preprocessing included realignment, slice timing correction, normalization to MNI space, and outlier regression via ART. The voxel-wise symmetric interhemispheric correlations were computed and included in the multiple regression analysis with age and sex covariates and the total volume of lesions as a regressor of interest. With a cluster-mass p-FDR corrected threshold ($p < 0.05$), inter-hemispheric correlation analysis revealed a cluster positively related to total lesion load in the left/right Precentral Gyrus ($T(15) = 5.12$, p-FDR < 0.00013). Thus, increased lesion burden is associated with changes in the sensorimotor integration. These findings demonstrate that structural lesion burden is independently tied to elevated precentral gyrus connectivity, suggesting a direct link between cumulative white matter damage and the recruitment of compensatory sensorimotor pathways.



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Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.12/Z18

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Longitudinal Analysis of Single MS CSF B-cells Reveals Clonal Persistence

Authors: *J. LIN, E. LYNCH, **E. BAGADE**, L. APELTSIN, S. A. SADIQ;
Tisch MS Res. Ctr., New York, NY

Abstract: MS CSF B-cell clonal expansion (2 or more cells with identical CDR3 regions) has been well documented in MS. However, whether the same clone can be detected over time in the same MS patient (clonal persistence) has not been well explored. We analyzed longitudinal CSF

samples from 5 MS patients for the presence of B-cell clonal persistence.
Single B-cells from MS CSF were sorted and their immunoglobulin genes sequence analyzed. Sequences were aligned to the online database, IMGT, and their CDR3 regions were used to determine clonality. Of the five patients, four had two CSF samples with time intervals between the two longitudinal samples ranging from 9 months, 19 months, 8 years, and 9 years. The remaining MS patient had four CSF samples analyzed over a 9-month time period.
We detected clonal expansion in all CSF samples. In the patient with four samples, the same clone was present in three of the samples while related clones were detectable in all four samples. In the patient with two samples, 9 months apart, identical clones were detected in both samples while related clones were also present in both samples. In the patients with samples 19 months apart and 8 years apart, multiple identical clones were present in both samples. Finally, in the patient with samples 9 years apart, no identical or related clones were detected.
We were able to detect clonal persistence in four of the five patients. While many of the samples were within less than 19 months of each other, clonal persistence was detectable in a patient with samples as far apart as eight years. While MS antigen specificity has eluded researchers through the years, the presence and the continued existence of the same or related B-cells longitudinally suggest an ongoing antigen driven response that may be directly involved in MS pathogenesis. Focusing on identifying the antigenic targets of these persistent cells may lead to greater success.

Disclosures: J. Lin: None. **E. Lynch:** None. **E. Bagade:** None. **L. Apeltsin:** None. **S.A. Sadiq:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

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Program #/Poster #: PSTR358.13/Z19

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R15NS133909

Title: Role of Hemoglobin Subunit Beta (Hbb) in Enhancing Mitochondrial Bioenergetics and Gene Regulation in Multiple Sclerosis

Authors: *P. RICHA[1], A. NAIR[1], B. NELSON[1], K. KNIES[1], J. MCDONOUGH[2];
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Abstract: Multiple sclerosis (MS) is characterized by demyelination and progressive neurological disability. Mitochondrial dysfunction is a key driver of MS-related pathology, which includes axonal damage and neuronal loss. Previous studies have reported defects in mitochondria in MS and decreased expression of electron transport chain genes as well as inhibition of respiratory complexes. Previous studies using rat primary neurons and postmortem MS brains showed changes in Hemoglobin subunit Beta (Hbb) interaction with mitochondrial

genes. Despite these findings, the exact function of Hbb in neurons is still not clear. We ligated the mouse Hbb gene into the pVITRO2 neo mcs mammalian expression vector. We then transfected pVITRO2-Hbb (n=4) and the pVITRO2-empty vector (n=4) into SH-SY5Y cells, a human derived neuroblastoma cell line. We performed Seahorse respirometry on the transfected cells, which is a technique that measures energy production on living cells. Respirometry data revealed increased mitochondrial respiration in the cells transfected with the pVITRO2-Hbb plasmid. The basal respiration, the ATP-linked OCR, and the maximal respiratory capacity were increased after Hbb overexpression. Proximity ligation assay (PLA) in mouse brains identified protein-protein interaction between Hbb and Ten Eleven translocation 1 (TET1), which plays a role in actively regulating gene expression. Based on the Seahorse respirometry and PLA data, we show that Hbb interaction with TET1 alters the catalytic function of TET1, causing changes in methylation patterns at the promoter of genes involved in mitochondrial bioenergetics. Statistical analysis was done using one-way ANOVA and student t-test, with $p \leq 0.05$ considered significant. Our data provide insights into the function of Hbb towards increasing mitochondrial bioenergetics, which is severely impaired in neurodegenerative diseases.

Disclosures: P. Richa: None. **A. Nair:** None. **B. Nelson:** None. **K. Knies:** None. **J. McDonough:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

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Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

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HHMI
AHA Predoctoral Grant 26PRE1564185
NIMH Predoctoral Grant 1F30MH144737-01

Title: Investigating the role of astrocyte-microglia crosstalk in cortical demyelination and myelin repair

Authors: *H. J. HEO[1], C. COLÓN ORTIZ[2], J. J. RAMIREZ[4], J. T. SAVAGE[3], C. EROGLU[1]; [1]Cell Biol., [2]Pediatrics, [3]Neurobio., Duke Univ., Durham, NC; [4]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Multiple sclerosis (MS) is a debilitating neuroinflammatory disease traditionally defined by white matter (WM) demyelination; however, extensive cortical grey matter (GM) pathology is now recognized as a major contributor to clinical disability. Yet, the mechanisms driving GM loss remain poorly understood. Emerging evidence implicates astrocytes and microglia as key regulators of myelin integrity, synaptic stability, and neuronal survival;

however, how astrocyte-microglia crosstalk coordinates cortical demyelination, synapse loss, and neurodegeneration and recovery in MS remains unknown. During postnatal visual cortex development, astrocyte-secreted Hevin (SPARCL1) induces a distinct microglial state marked by elevated TLR2 expression. These phagocytic “TLR2-high” microglia are required for thalamocortical synapse elimination and exhibit transcriptional features of remyelination-linked microglia. We therefore hypothesized that astrocyte-microglia signaling via Hevin may be re-engaged during demyelination and contribute to myelin and synapse recovery. To test this, we established a robust model of GM demyelination and recovery in the visual cortex using cuprizone administration. Using this model, we observed pronounced astrocyte reactivity, marked by increased GFAP expression, alongside microglial activation characterized by loss of homeostatic marker P2RY12, specifically within the deep cortical layers during demyelination and remyelination. We also found specific loss of thalamocortical synapses during both demyelination and remyelination. Notably, in cuprizone-treated mice with a TLR2-HA reporter, we detected a prominent induction of TLR2-high microglia selectively during remyelination. These microglia had elevated phagocytic activity, as indicated by increased CD68 expression. Importantly, this remyelination-associated induction of TLR2-high microglia was dependent on Hevin, as this phenotype was absent in Hevin knockout mice. To further define these glial states and their molecular underpinnings, we performed glia-enriched single-nucleus RNA sequencing of the visual cortex from control and cuprizone-remyelination animals. We find that remyelination-associated glia exhibit increases in interferon signaling, and that microglia specifically upregulate genes involved in synaptic regulation. Overall, these findings suggest that developmental astrocyte-microglia signaling pathways are reactivated during cortical remyelination and uncover a previously unrecognized glial-glial signaling axis during GM recovery that may reveal new therapeutic targets to enhance cortical repair in MS.

Disclosures: H.J. Heo: None. **C. Colón Ortiz:** None. **J.J. Ramirez:** None. **J.T. Savage:** None. **C. Eroglu:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.15/Z21

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R35NS132150
NIH Grant R01NS096748
NIH Grant R01NS109670
Conrad N. Hilton Foundation #17734
Conrad N. Hilton Foundation #18394

Title: APOEε4 Drives Sex-Specific Microglial Dysregulation and Neuronal Vulnerability in Experimental Autoimmune Encephalomyelitis

Authors: *J. ALGA-SHERIFF, Y. ITOH, N. ITOH, S. GUNE, N. XIE, R. VOSKUHL; Dept. of Neurol., UCLA, Los Angeles, CA

Abstract: Multiple sclerosis (MS) and Alzheimer's disease (AD) are neurodegenerative diseases influenced by sex. MS affects women compared to men at a ratio of nearly 3:1. Lifetime AD risk is nearly double in females. Microglia are critical mediators of neuroinflammation and neurodegeneration and can exhibit sex-dependent changes in activation. Apolipoprotein E ε4 (APOEε4) is the strongest genetic risk factor for late-onset AD, and humanized APOE (hAPOE) models provide a tool for investigating how APOE variants influence disease in mice. Experimental autoimmune encephalomyelitis (EAE) is a well-established model for neuroinflammation and neuroaxonal degeneration in MS. Here, how APOE genotype (ε3 vs. ε4) and sex influence EAE course and neuropathology was examined. EAE was induced in young (4- to 5-month), female and male, APOEε3 and APOEε4 mice. Immunohistochemistry characterized neuropathology with markers for myelin (Myelin Basic Protein, MBP), axons (Neurofilament 200, NF200), axonal damage (Beta-Amyloid Precursor Protein, β-APP), T-cells (Cluster of Differentiation 3, CD3), neurons (Neuronal Nuclei, NeuN), and microglia/macrophage activation (Ionized Calcium-Binding Adapter Molecule 1, IBA1; Major Histocompatibility Complex Class II, MHCII). Results showed that APOEε4 had worse EAE walking scores than APOEε3 in females, while there was no genotype effect in males. Immunohistochemistry of spinal cord white matter showed that APOEε4 EAE females demonstrated higher $IBA1^+$ area fraction than APOEε3 EAE females, while males showed no genotype difference. Both sexes had similar levels of myelin, axons, and T cell infiltration in EAE when comparing the two genotypes. In spinal cord gray matter, there were robust elevations in $MHCII^+IBA1^+$ in EAE in both genotypes. However, APOEε4 healthy control females demonstrated higher $MHCII^+IBA1^+$ area fraction than APOEε3 control females. Beyond microglia, $NeuN^+$ staining was lower in APOEε4 EAE females versus APOEε3 EAE females. Given the differences in spinal cord gray matter, we then examined thalamic gray matter. Thalamic gray matter showed the same pattern of EAE-induced microglial activation as in spinal cord gray matter, with higher $MHCII^+IBA1^+$ area fraction in APOEε4 healthy control females compared to APOEε3 control females. Together, these findings suggest APOEε4 drives higher microglial activation in the gray matter of females as compared to males during health, aligning with worse neuronal loss in APOEε4 females during disease. These results highlight APOEε4, sex, and neuroinflammatory dysregulation as interacting determinants of neuropathology, with implications for MS and AD.

Disclosures: J. Alga-Sheriff: None. **Y. Itoh:** None. **N. Itoh:** None. **S. Gune:** None. **N. Xie:** None. **R. Voskuhl:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

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Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R35NS132150
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NIH Grant R01NS109670
Conrad N. Hilton Foundation #17734
Conrad N. Hilton Foundation #18394

Title: Region- and Sex- Specific Microglial Responses to Disease and Age in a Mouse Model of Multiple Sclerosis

Authors: *D. HEBBAR, N. ITOH, N. HIGGINS, R. LI, R. SHEHADEH, Y. ITOH, R. VOSKUHL;
Dept. of Neurol., UCLA, Los Angeles, CA

Abstract: Progressive disability in multiple sclerosis (MS) worsens with age and is linked to gray matter neurodegeneration. The thalamus, a central hub for cognitive and motor function, is among the earliest affected. Thalamic atrophy has been associated with clinical disability. However, whether age-related microglial changes occur in thalamus in MS remains unclear. The spinal cord white matter was examined as a well characterized comparator region. Here, sex-matched young (3-4 months) and midlife (12-14 months) C57BL/6J mice, including healthy controls and experimental autoimmune encephalomyelitis (EAE) mice, were analyzed. Thalamus and spinal cord sections were examined by immunofluorescence for microglia using Ionized calcium-binding adaptor molecule 1 (IBA1), Major Histocompatibility Complex Class II (MHCII), Cluster of Differentiation 68 (CD68), C-type lectin domain family 7 member A (CLEC7A), and Apolipoprotein E (APOE), astrocytes using Glial fibrillary acidic protein (GFAP) and Lipocalin-2 (LCN2), synapses using vesicular glutamate transporter 2 (VGLUT2) and Postsynaptic Density Protein 95 (PSD95), axonal injury using Beta-Amyloid Precursor Protein (βAPP), and T cell infiltration using Cluster of Differentiation 3 (CD3). Results showed that midlife mice had worse EAE walking scores as compared to young mice in both females and males. As expected, in EAE spinal cord white matter, there was an increase in activated microglia, disease associated microglia, T cell infiltration, and axonal damage. This occurred equally in both females and males. Interestingly, in the thalamus there were major effects of age, with minimal effects of EAE. Specifically in midlife mice compared to young mice there was increased activated, phagocytic, and disease-associated microglia, reactive astrocytes, and synaptic loss, in both females and males. Notably, EAE compared to healthy mice did not show differences in any of the above markers in the thalamus at either young or midlife ages. Together these findings indicate that midlife EAE mice with walking disability have spinal cord pathology driven by disease and thalamic pathology driven by age.

Disclosures: D. Hebbar: None. **N. Itoh:** None. **N. Higgins:** None. **R. Li:** None. **R. Shehadeh:** None. **Y. Itoh:** None. **R. Voskuhl:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.17/Z23

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Tisch MSRCNY (private funding)

Title: Investigating Cognitive Dysfunction in Multiple Sclerosis using Human iPSC-derived Cerebral Organoids

Authors: *K. KALPANA, N. SILVERMAN-LLOYD, S. A. SADIQ;
Tisch Multiple Sclerosis Res. Ctr. of New York, New York, NY

Abstract: Multiple Sclerosis (MS) is a demyelinating, neuroinflammatory and neurodegenerative disease of the brain and spinal cord, affecting 3 million people in the world and nearly 1 million in the US. Cognitive impairment (CI) is a particularly debilitating symptom of MS that affects 40-70% of all MS patients. It can often start in the early stages of the disease, even in the absence of other neurological defects. CI progresses with age, leading to a decline in cognitive functions such as information processing speed, episodic memory, and executive functions, and affecting their daily activities. 10% of patients affected by CI experience severe cognitive decline. Current diagnosis of CI relies on clinical MRIs and cognitive battery tests performed by neuropsychologists. However, due to the variability in MS patients affected by CI, the causes and mechanisms behind CI are poorly understood. Current animal and *in vitro* models fail to capture the complex neurodegenerative and inflammatory processes that contribute to cognitive decline in MS. We investigated whether the cerebrospinal fluid (CSF) derived from MS patients with CI may help better explain the biological basis of the disorder. We used 3D cerebral organoid models generated from healthy induced pluripotent stem cells (iPSCs) to investigate the causes of CI in MS by exposing them to CSF from cognitively impaired (CI) as well as patients without cognitive impairment. Using immunofluorescence (IF) and electrophysiology using multi-electrode array (MEA), we are identifying differential patterns between with and without CI conditions. Preliminary results using IF revealed some differences in the neurodegeneration patterns between with and without CI. We observed the effects of CSF on organoids at two time points- 24 hours for acute and 6 days for chronic exposure. The organoids with chronic exposure to CI CSF showed loss of pan-neuronal marker, microtubule-associated protein 2, MAP2 as well as fragmented neuron-specific beta-III tubulin, Tuj1 expression compared to both organoids exposed to CSF of patients without CI and media controls. We also observed an increase in degenerating neurons in organoids exposed to CI CSF with fluoro-jade C (FJC) staining. We have demonstrated differences between with and without CI in MS using novel and innovative approaches such as CSF exposure to cerebral organoids. This work is an initial exploration to understand the biological basis of CI in MS, but additional studies are still needed using a larger sample cohort. By integrating CSF from patients with CI with human iPSC-derived cerebral organoids, we possibly have a tentative model of MS-associated cognitive dysfunction.

Disclosures: K. Kalpana: None. **N. Silverman-Lloyd:** None. **S.A. Sadiq:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.18/Z24

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R15NS133909

Title: Voluntary running promotes an increase in BCAS1+ newly formed oligodendrocytes in the aging mouse brain

Authors: *A. NAIR[1], P. RICHA[1], B. NELSON[1], K. KNIES[1], N. AL RAMEL[1], M. ADESINA[2], E. M. MINTZ[3], M. SHALIH MARAICAR[1], J. MCDONOUGH[4];
[2]Biol. sciences, [3]Col. of Arts & Sci., [4]Biomed. Sci., [1]Kent State Univ., Kent, OH

Abstract: A major hallmark of both normal aging and neurological diseases is loss of myelin integrity, yet the cellular mechanisms promoting myelination are not fully understood. Oligodendrocyte differentiation is a rate-limiting step in remyelination and is important for the repair of the central nervous system (CNS) in diseases like multiple sclerosis (MS). Successful remyelination requires the oligodendrocyte precursor cells (OPCs) to not only attempt to differentiate but also to complete it, forming oligodendrocytes capable of producing myelin. Physical exercise has shown great potential in promoting remyelination, but whether it does so by increasing OPC differentiation attempts or improving their success rates is not fully understood. In this study, we aim to determine whether voluntary running alters oligodendrocyte differentiation dynamics in the adult brain. We used six-month-old male C57BL/6 mice and subjected them to four weeks of voluntary wheel running as an exercise paradigm. Brain sections from the cortex and striatum were stained with a combination of immunohistochemical markers, such as chondroitin sulfate (CS56) to label the dandelion clock-like structures (DACS) associated with extracellular matrix changes marking oligodendrocyte differentiation attempts, and breast carcinoma amplified sequence 1 (BCAS1) to label newly formed oligodendrocytes marking successful differentiation. Cell densities were calculated between running vs sedentary controls and analysed using an unpaired t-test with data expressed as mean ± SD, and $p < 0.05$ is considered significant (n=4 per group). Preliminary data show a non-significant increasing trend in the CS56+ cell density in both striatum (929 ± 335 vs 1320 ± 190 cells/mm³, p=0.101) and cortex (864 ± 267 vs 1245 ± 62 cells/mm³, p=0.061) in the running group as compared to controls. We also see a significant increase in the BCAS1+ cell density in both striatum (3278 ± 248 vs 4893 ± 207 cells/mm³, p<0.001) and cortex (2839 ± 262 vs 4331 ± 252 cells/mm³, p<0.001) in the running group as compared to the control. Together, these preliminary findings suggest that voluntary running may increase the success of differentiation attempts, producing newly formed oligodendrocytes, with the possibility of increasing the number of differentiation attempts. Future studies will examine sex-specific differences in this response.

Disclosures: A. Nair: None. **P. Richa:** None. **B. Nelson:** None. **K. Knies:** None. **N. Al Ramel:** None. **M. Adesina:** None. **E.M. Mintz:** None. **M. Shalih Maraicar:** None. **J. McDonough:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.19/AA1

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

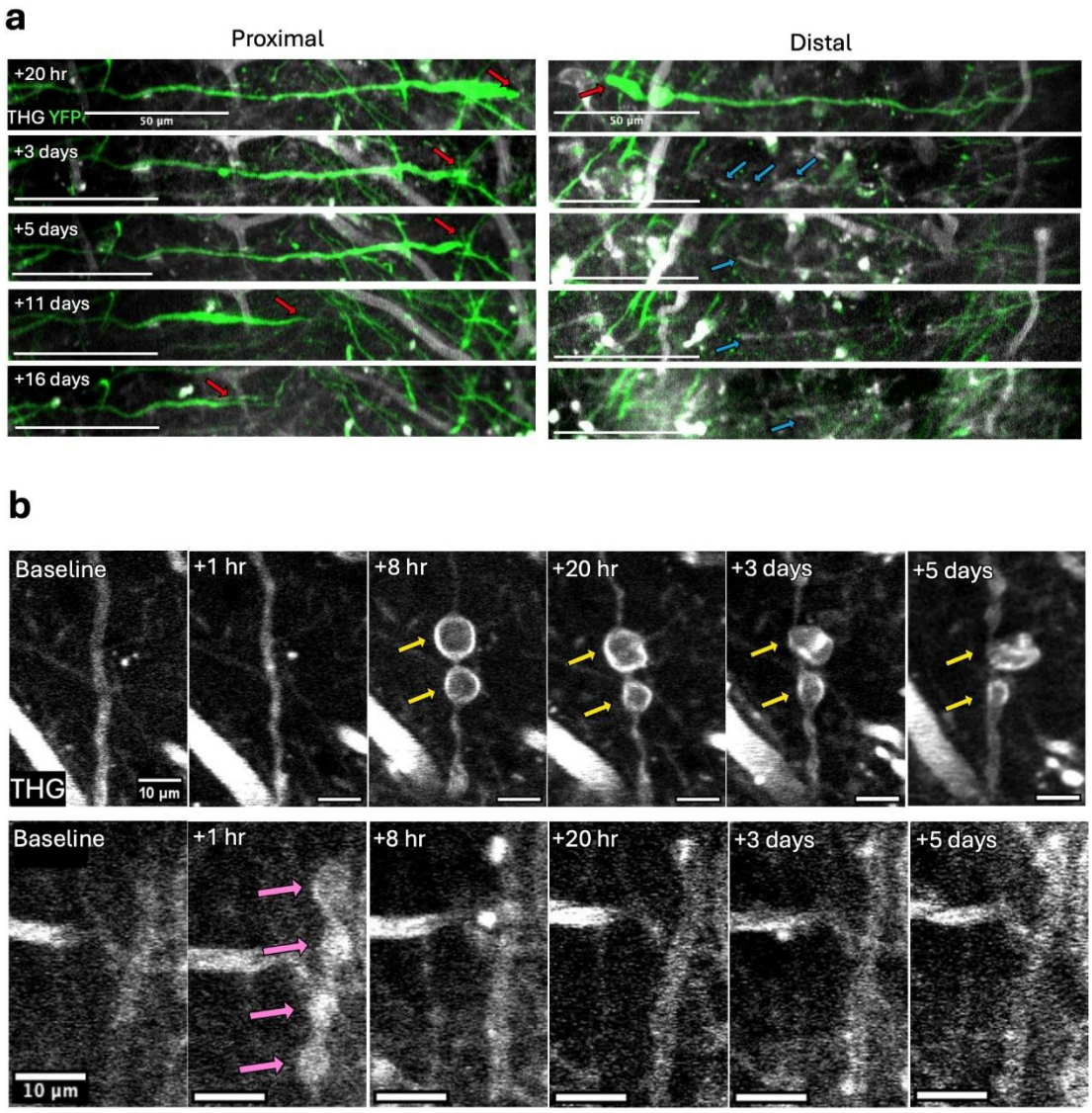
Title: Tracking the degeneration of laser-ablated myelinated axons in the mouse cortex using in vivo three-photon microscopy

Authors: *E. L. LE, R. F. HAWKINS, C. B. SCHAFFER, N. NISHIMURA;
Meinig Sch. of Biomed. Engin., Cornell Univ., Ithaca, NY

Abstract: Maintenance of axon and myelin integrity is critical for neural communication and their degeneration is a hallmark of neurodegenerative diseases. Existing injury models cause widespread damage that limits investigation into early degenerative events at the single-axon level. To address this limitation, we used in vivo, amplified femtosecond laser ablation to selectively sever single myelinated cortical axons in mice expressing yellow fluorescent protein (YFP) in neurons. We combined multiphoton fluorescence imaging with third harmonic generation (THG) microscopy to simultaneously monitor axonal integrity and myelin morphology over time.

Axons displayed canonical Wallerian degeneration, in which axonal segments visualized with cytoplasmic YFP (green) slowly retracted on one side (panel a, red arrows), presumed to be proximal and connected to the soma, while distal segments fragmented rapidly. Further, we found myelin degeneration appeared partially decoupled from axonal degeneration. Even after axonal fluorescence had largely disappeared, myelin remnants remained detectable with altered morphology or as debris-like structures (panel a, blue arrows).

Thick (~1.5 μm FWHM) and thin (~1.0 μm FWHM) axons displayed distinct myelin remodeling dynamics. Thicker axons developed numerous transient myelin swellings within hours after injury, including in sheaths not directly adjacent to the ablation site, hundreds of micrometers away. Most small swellings (~4 μm diameter, panel b, top; yellow arrows) resolved within one day, while larger swellings (~10 μm, panel b, bottom; pink arrows) persisted for several days and were frequently localized to regions of severe axonal pathology. In contrast, thin axons developed substantially fewer swellings, which were typically small and transient. Together, these findings establish a high-resolution experimental framework for studying mechanisms of myelin remodeling, debris clearance, and repair after injury.



Disclosures: E.L. Le: None. **R.F. Hawkins:** None. **C.B. Schaffer:** None. **N. Nishimura:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.20/AA2

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Single-Section Spatial Multiomics Reveals Neuroinflammatory and Demyelinating Pathology in the EAE Mouse Model

Authors: C. MILLOT[1], S. FIGUEREDO[2], S. KAUR[3], *D. WAKHLOO[2], **A. DIKSHIT**[2]; [1]Inotiv, Longmont, CO; [2]Bio-Techne Spatial, Newark, CA; [3]Bio-Techne Spatial, Denton, TX

Abstract: Conventional spatial imaging approaches are typically limited to the analysis of either protein or RNA, restricting comprehensive molecular characterization within tissue sections. The central nervous system is defined by spatial organization where the cellular localization determines function. Detecting RNA and protein in the same section, at single-cell resolution, is the only way to connect transcriptional state to functional output without losing the spatial context. The RNAscope™ Multiomic LS Fluorescent Assay enables simultaneous detection of protein and RNA within a single tissue section, improving colocalization and multiplexing capabilities. In this study, the Multiomic platform was applied to spinal columns from Inotiv's Experimental Autoimmune Encephalomyelitis (EAE) mouse model of demyelination. Multiple protein (i.e., MOG, Iba-1, and GFAP) and RNA targets (e.g., IL-1β, IL-6, and TNF-α) associated with neuroinflammation and myelin integrity were visualized using ACD's proprietary ZZ chemistry followed by Opal dye tyramide signal amplification. Co-detection of protein and RNA targets illustrates disease pathology in the model, highlighting the extent of spatial information that can be generated with a single slide. The increase in Iba-1 and GFAP with decreased MOG expression observed in this study pointed to the expected neuroinflammation and demyelination associated with the disease pathology of the model.Visualizing multiple different targets on a single slide allows for tissue preservation and a better understanding of target interactions during disease progression while in some cases reducing costs.

Disclosures: S. FIgueredo: A. Employment/Salary (full or part-time):; Bio-Techne. **S. Kaur:** A. Employment/Salary (full or part-time):; Bio-Techne. **D. Wakhloo:** A. Employment/Salary (full or part-time):; Bio-Techne. **A. Dikshit:** A. Employment/Salary (full or part-time):; Bio-Techne.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.21/AA3

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: Ralph W. and Grace M. Showalter Research Trust

Title: PFAS exposure in the rat brain reveals dysfunctional bile acid metabolism and bioenergetic changes

Authors: *J. PARK[1,2], B. JIANG[2,1], J. R. CANNON[2,1], P. BALONI[2,1];
[2]Sch. of Hlth. Sci., [1]Purdue Univ., West Lafayette, IN

Abstract: Poly- and perfluoroalkyl substances (PFAS) have been widely detected in the human blood globally. PFAS congeners have been reported to accumulate in lipid-rich organs, such as the brain, and have been well-studied for their role in metabolic dysregulation. However, PFAS induced metabolic dysregulation and neurotoxicity in the brain have not been completely characterized. Sprague-Dawley rats (n=12) were exposed to PFOS (10mg/kg) once and sacrificed at day 112. Brain tissue from control and PFOS-exposed rats were subjected to RNA sequencing. We used DeSeq2 to identify differentially expressed genes between PFOS-exposed and control. We integrated the transcriptome data with the rat genome scale metabolic model (GEM) Rat-GEM and performed flux balance analysis to explore the metabolic alterations in the brain. The genes associated with the disrupted metabolic reactions were enriched using Reactome. We performed flux balance analysis and selected top 1000 metabolic reactions based on flux differences between the PFOS and control group, determined by Kolmogorov-Smirnov test (FDR threshold 0.05). These reactions belonged to fatty acid oxidation, energy metabolism, bile acid biosynthesis, and prostaglandin biosynthesis pathways. We extracted metabolic genes corresponding to the top 20 subsystems and found fatty acid metabolism, triglyceride catabolism, metabolism of nucleotides, retinoic acid (RA) biosynthesis pathway, and arachidonate metabolism to be enriched in our analysis. Metabolic modeling and differential expression analyses identified key genes in solute carrier (SLC)-mediated transmembrane transport (*Scl43a1, Slc4a5, Slc29a4, and Slco1a4*), and visual phototransduction and sensory perception (*Rbp3 and Dhrs3*). We compared our PFOS-affected metabolic genes with nominated Alzheimer's disease genes from Agora database, and identified *SLCO1A2* and *CYP27A1*, which are involved in bile acid and bile salt metabolism. Using integrated genome-scale metabolic model, our study identified PFAS associated metabolic dysregulation especially for bioenergetic pathways in the rat brain. Our analysis also revealed genes involved in bile acid metabolism that are impaired due to PFAS exposure and had a strong connection with Alzheimer's disease pathophysiology.

Disclosures: J. Park: None. **B. Jiang:** None. **J.R. Cannon:** None. **P. Baloni:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.22/AA4

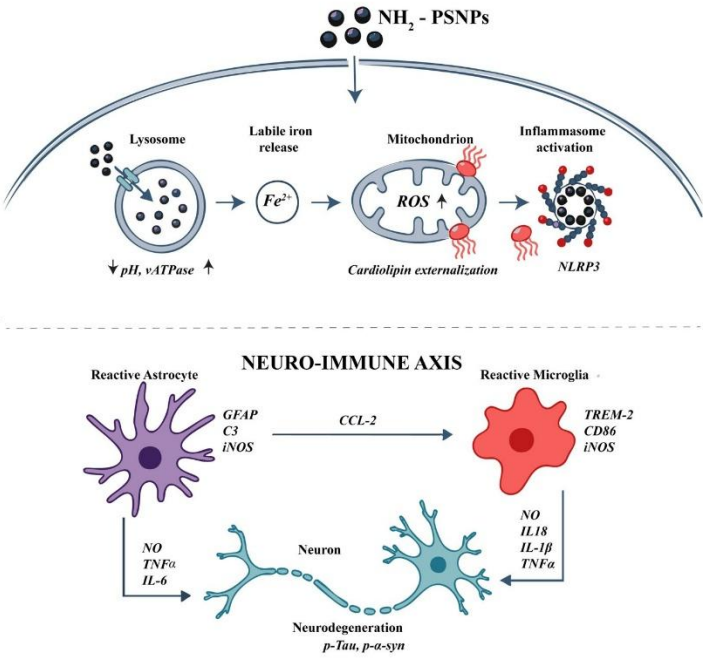
Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: (MSIT) (RS-2024-00336758)
Fourth Stage of Brain Korea 21

Title: Nanoplastics drive glial iron-inflammasome signaling and proteinopathy in a human neuro-immune model

Authors: ***A. JAMSRANJAV**[1], M. TRAN[2], K. V. DO[3], H. CHO[4];
[1]Inst. of quantum biophysics, Suwon, Korea, Republic of; [2]Dept. of Biophysics, Sungkwunkwan Univ., Suwon, Korea, Republic of; [3]Intelligent Precision Healthcare Convergence, Sungkyunkwan Univ., Suwon, KS; [4]Biophysics, Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Micro- and nanoplastics have been detected in human brain tissue, raising questions about their possible relevance to brain health and neurodegenerative vulnerability. However, the mechanisms linking nanoplastic exposure to neuroinflammation and neuronal proteinopathy remain poorly understood. Here, we explored the mechanism of nanoplastic-induced neuropathology using a nanoplastic-infiltrated human neuro-immune axis (NP-hNIA) model. We found that amine-coated polystyrene nanoplastics (PS-NPs) were preferentially engulfed by neuroglia, where their bioreactive surfaces induced v-ATPase-mediated lysosomal hyperacidification, labile iron leakage, cardiolipin externalization, and NLRP3 inflammasome activation. The astrocytic inflammasome subsequently triggered the release of pro-inflammatory mediators, including CCL2, IL-6, and TNF-α, which primed microglia and established a feed-forward neuroinflammatory loop. This synergistic glial inflammation was associated with multiple hallmarks of neuropathology, including tau hyperphosphorylation, α-synuclein aggregation, and synaptic loss. Notably, 810-nm photobiomodulation (PBM) selectively restored mitochondrial integrity and attenuated inflammatory activation, while lysosomal alterations remained largely unresolved. Our findings suggest that the signaling of lysosome damage-mitochondrial damage-neuroinflammation could be a key axis in nanoplastics-associated neuronal proteinopathies.



Disclosures: A. Jamsranjav: None. **M. Tran:** None. **K.V. Do:** None. **H. Cho:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.23/AA5

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Mass. Life Science Center Bits to Bytes

Title: Investigating the role of microglia in MS via cell type and environment aware functional genomics in vitro

Authors: *X. LUNA[1,3], M. D. GALLAGHER[3], O. CORRADIN[3,2];
[1]Brain and Cognitive Sci., [2]Biol., MIT, Cambridge, MA; [3]Whitehead Inst., Cambridge, MA

Abstract: The pathogenesis of complex traits like multiple sclerosis (MS) involves disruption of many cell types and systems. However, functional studies that aim to characterize the impact of disease-associated SNPs often investigate all SNPs in the same cellular context. MS is both an autoimmune and neurodegenerative disease, but the role of CNS cells in MS pathogenesis remains poorly understood. Here, we integrate a computational approach to predict the MS genetic risk loci that act within the brain with functional CRISPR perturbation studies in iPSC-derived microglia cells (iMGL). We previously developed an approach that leverages the cell-type-specificity of cis regulatory elements (CREs) to pinpoint the cell types that are most impacted by specific non-protein coding disease-linked alleles. Applying this method to MS risk alleles, we identified 44 loci predicted to influence CNS cells, including 17 loci in microglia. We performed Perturb-seq, pooled CRISPR inhibition followed by single cell RNA-seq, to investigate the impact of 34 cis regulatory elements associated with MS risk loci in iMGL. We identified the target genes and downstream differentially expressed genes (DEGs) for 5 independent GWAS loci. Importantly, these DEGs were substantially enriched for MS heritability. DEGs from all 5 target genes show significant overlap, converging on downregulation of cytokinesis and phagocytosis, and upregulation of mitochondrial metabolism. We then compared DEGs to gene expression patterns in MS patient tissue and observed striking similarities, demonstrating that genes dysregulated as the result of GWAS loci perturbation mirrored effects observed in microglia in MS lesions. This strategy enabled us to focus on the subset of MS GWAS loci that disrupt gene regulation in microglia, and revealed highly convergent biological mechanisms of GWAS loci in these cells. In addition to the context of cell type, activity of CREs is also highly influenced by cellular environment. To investigate the impact of environmental stimuli on microglia CREs we performed H3K27ac ChIP-seq on iMGLs exposed to MS-relevant cytokine, protein, and lipid stimuli. We identified substantial epigenetic changes surrounding MS risk loci, demonstrating the importance of cellular and environmental contexts in the study of noncoding genetic risk loci linked to disease. Collectively, these results demonstrate how cell type and environment aware functional studies

can reveal new insights into complex trait pathogenesis and elucidate convergent biological mechanisms.

Disclosures: X. Luna: None. **M.D. Gallagher:** None. **O. Corradin:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.24/AA6

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Role of integrated stress kinase HRI in an EAE model of Multiple Sclerosis

Authors: *D. MOHAN[1,2], M. HETMAN[3,1,4], S. SARASWAT[3,2];
[1]Anatom. sciences and neurobiology, [2]Kentucky spinal cord injury, [3]Neurolog. Surgery, [4]Pharmocology and Toxicology, Univ. of Louisville, Louisville, KY

Abstract: Role of the integrated stress response kinase HRI/EIF2AK1 in an EAE model of Multiple Sclerosis Mohan D[1,2], Mathew M[2], Andres KR[2], Russel M Howard RM[2], Zheng J[5], Hetman M[2,3,4], Saraswat Ohri S[2,3] Graduate Program in Anatomical Sciences and Neurobiology[1], Kentucky Spinal Cord Injury Research Center[2], UofL Department of Neurological Surgery[3],Pharmocology and toxicology[4],Microbiology and immunology[5] Experimental autoimmune encephalomyelitis (EAE) results in inflammatory damage of the white matter that resembles multiple sclerosis (MS). Heme regulated inhibitor (HRI) is a protein kinase that initiates the integrated stress response (ISR) pathway under heme deficiency, mitochondrial stress or cytosolic protein aggregation . In the latter context, HRI supports innate immunity promoting anti-bacterial defenses, but also, may enhance secondary damage of host tissues. Our recent preliminary data show attenuated EAE severity in mice with a germline deletion of the Hri/Eif2ak1 gene ($Hri^{-/-}$). This correlates with reduced transcript levels of proinflammatory cytokines (*Tnf-α, Il-1β, Il-6, and Nos2*) and increased transcript levels of oligodendrocyte markers (*Mbp, Plp*) in $Hri^{-/-}$ mice after EAE induction. Interestingly, $Hri^{-/-}$ mice show expanded CD8 T cell population in the spinal cord including a Rorg/Tbet double positive cells. Conversely, innate immune cells numbers are unaffected. Therefore, the attenuated EAE phenotype may be a consequence of increased presence/activity of the regulatory CD8 T cells that suppress autoimmune activation of CD4 T cells. These data suggest that HRI plays a detrimental role in the autoimmune neuroinflammation that is driven by the positive regulation of the adaptive immune response.

Disclosures: D. Mohan: None. **M. Hetman:** None. **S. Saraswat:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.25/AA7

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH-NINDS Grant 2R56NS107523-06
NIH Grant TL1TR001431

Title: Comparative single-cell transcriptomics of neuroinflammation in preclinical mouse models of Multiple Sclerosis (MS) and MS Tissue

Authors: *M. R. BULLARD, G. S. MELCHOR, Jr., J. K. HUANG;
Biol., Georgetown Univ., Washington, DC

Abstract: Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS affecting over 2.8 million people worldwide, characterized by neuroinflammatory lesions in which remyelination initially occurs but ultimately fails. This failure to remyelinate is thought to be due in part to a complex neuroinflammatory lesion niche comprised of resident microglia and recruited peripheral immune cells which possess highly heterogeneous transcriptional states spanning pro-inflammatory and pro-regenerative profiles. Yet the cell-type specific mechanisms governing this niche and their contributions to demyelination and remyelination remain poorly understood, limiting therapeutic development. Equally limiting is uncertainty about how faithfully standard preclinical models recapitulate human MS immunopathology at the cellular level, particularly given the distinct immune niches these models engage that span adaptive and innate immunity, the spinal cord, and brain, making any molecular signal conserved across these distinct contexts unlikely to reflect model-specific immune responses.

To address this, we integrated 8 publicly available single-nucleus and single-cell RNA sequencing (sn/scRNA-seq) datasets. This multi-model framework spans post-mortem human MS brain tissue and three standard preclinical mouse models: Experimental Autoimmune Encephalomyelitis (EAE), lysolecithin-induced demyelination (LPC), and cuprizone-induced demyelination (CPZ).

Our integration identifies a core conserved inflammatory signature shared across all models and human MS tissue, marked by upregulation of genes mediating hypoxic stress response and lysosomal activity alongside coordinated downregulation of microglial homeostatic markers. This convergent departure from surveillant microglial identity is observed across mechanistically distinct models engaging different immune niches. This points to a core neuroinflammatory response shared across distinct experimental contexts. Preliminary analyses also further implicate phagocytic and ferroptotic pathway dysregulation within demyelinating environments. We additionally identify candidate genes reproducibly dysregulated across conditions that warrant future investigation.

Together, this cross-species framework for translating mouse model findings to human MS provides a foundation for identifying and prioritizing cell-type-specific therapeutic targets aimed at restoring immune homeostasis and rescuing remyelination.

Disclosures: M.R. Bullard: None. **G.S. Melchor:** None. **J.K. Huang:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.26/AA8

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: 7,8-dihydroxyflavone (DHF) treatment protects against optic neuritis and retinal damage in an animal model of Multiple Sclerosis.

Authors: T. K. MAKAR[1], ***F. J. DENARO**[2], S. MAKAR[3], A. N. PATEL[4], M. D. WORTHINGTON[2], S. WILLIAMS[2], J. BRYANT[5];
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Abstract: The pathology of multiple sclerosis (MS) includes inflammation, demyelination and neurodegeneration. A common symptom is inflammation of the optic nerve (ON). Neuronal loss and visual impairment can occur in a single episode. Repeated episodes can lead to ON atrophy with permanent visual symptoms. Immune modulating treatments have been ineffective in preventing neuronal loss or visual impairment. The examination of neuroprotective medicines is a promising adjunct. It was reported that: 7,8-dihydroxyflavone (DHF), has potent Brain-Derived Neurotrophic Factor (BDNF) agonist activity. Given orally it can readily cross the Blood Brain Barrier. Our hypothesis is that DHF treatment will minimize optic nerve and retinal damage with improved vision. This was tested in the Experimental Autoimmune Encephalomyelitis (EAE) model in which neuropathology and inflammatory markers were measured. We induced EAE in 2 groups of C57BL/6 mice (both male and female) by immunization with myelin oligodendroglia protein (MOG) peptide 35-55 using an established protocol. Mice were randomized to a control vehicle or treatment. DHF (5 mg/kg) was given daily by intraperitoneal injection started on the day of symptom onset. We scored EAE clinical severity using an established scale daily. We euthanized mice on day 40 (from EAE induction) and studied optic nerve and retinal tissues pathologically and immunohistochemically to determine the expression of different proteins including CD45+, CD3, CD20, TrkB, GFAP, axonal marker, inflammatory proteins. Microscopic images were analyzed for intensity of labeling and Prism Software was used to determine statistical differences of the labeling. Histological analysis of the ON with markers for CD45+, CD3+ and CD20+ revealed that infiltrated lymphocytes in EAE optic nerve were diminished. Phospho-TrkB showed up-regulation and demyelination was decreased. Our preliminary observations show that DHF treatment from the onset of EAE disease reduced the neurologic symptoms and the severity of EAE paralysis in C57Bl/6 mice. This was accompanied by decreased optic pathology. Based on these results, we propose that there are at least two possible mechanisms through which DHF reduces clinical severity and neuropathology. It could

reduce axonal damage and demyelination through a TrkB mediated effect on inflammatory cells, or it could have a direct TrkB mediated protective effect on neuronal cells. Such studies as this suggest that treatment of this disease could benefit from multiple approaches.

Disclosures: T.K. Makar: None. **F.J. Denaro:** None. **S. Makar:** None. **A.N. Patel:** None. **M.D. Worthington:** None. **S. Williams:** None. **J. bryant:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.27/AA9

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: IPN T32

Title: Investigating the role of disease associated oligodendrocytes in demyelination

Authors: *C. M. FRANCESCUTTI[1], Z. MANAVI[2], J. K. HUANG[3];
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Abstract: Disease associated oligodendrocytes (DAOs) have only recently been described in the context of Alzheimer's disease and multiple sclerosis (MS) in humans and mouse models and their role in neuroinflammatory conditions is currently unknown. It has been shown that DAOs secrete SERPINA3N, an inhibitor of granzyme B which induces apoptosis, suggesting that DAOs may have neuroprotective functions. However, it has also been shown via single-cell RNA sequencing that DAOs are implicated in neuroinflammatory pathways. Thus, it is crucial to identify the function of DAOs to determine whether they can be a therapeutic target in neuroinflammatory conditions. In this research proposal I hypothesize that central nervous system inflammation leads to DAO formation, that DAOs contribute to demyelinating pathology that leads to neurodegeneration. This will be investigated using a mouse model of chronic MS, myelin oligodendrocyte glycoprotein (MOG_{35-55}) mediated experimental autoimmune encephalomyelitis (EAE) in *Gamt* -GFP mice. GAMT is expressed in mature oligodendrocytes (OLs) when they are actively myelinating axons and preliminary data from our lab has shown that *Gamt* -GFP expression appears to be restricted to DAOs, as indicated by co-localization with SERPINA3N staining, rather than CC1-positive mature OLs that are normally seen in successfully remyelinating lesions.

Disclosures: C.M. Francescutti: None. **Z. Manavi:** None. **J.K. Huang:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.28/AA10

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Astrocyte-derived Endothelin-1 (ET-1) is a key negative regulator of remyelination associated with Multiple Sclerosis

Authors: *T. K. MAKAR[1], K. KELEDJIAN[2], M. I. AJIBOLA[3], I. J. MERCHENTHALER[4], J. BRYANT[5], V. GERZANICH[2];
[1]Epidemiology and Toxicology, Univ. of Maryland Sch. of Med., Gaithersburg, MD; [2]Neurosurg., Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Dept. of Psychiatry, Univ. of Maryland, Baltimore, Baltimore, MD; [4]Epidemiology & Publ. Hlth., Univ. of Maryland, Baltimore, MD; [5]Inst. of Human Virology, Univ. of Maryalnd, Baltimore, MD

Abstract: Introduction: Current multiple sclerosis (MS) therapies partially affect patients with relapsing and remitting MS but have little impact in promoting re-myelination in the demyelinated tissues. Endothelin -1 (ET-1) is highly expressed in the reactive astrocytes surrounding demyelinated lesions where it acts as a potent inhibitor of the re-myelinization. ET-1 secreted by astrocytes halts transition of the of oligodendrocyte progenitor cells (OPCs) into mature myelin-producing oligodendrocytes. Our recent work showed that Sur-1 inhibitor Glibenclamide (GLB) has beneficial effects during chronic phase of the murine experimental autoimmune encephalomyelitis (EAE) acting as a suppressor of the reactive gliosis. The objective of this study was to evaluate effect of GLB on ET-1 production in reactive astrocytes and the impact on re-myelinization in EAE models. **Methods:** EAE was induced in 2 groups of C57Bl/6 8-week old female mice by immunization with myelin oligodendroglial protein peptide 35-55 using an established protocol. Mice were randomized for either vehicle or GLB (10 ug/d) treatment given daily by intraperitoneal injection started on the day of symptoms onset. We scored EAE clinical severity daily using an established scale. Mice were euthanized on day 40 (from EAE induction) and spinal cord tissues were studied using histological and immunohistochemical methods to determine the expression of the markers of the astrocyte activation, ET-1 production and oligodendrocyte involvement in remyelination. **Results:** Immunohistochemical studies of the EAE spinal cords showed reactive astrocytosis, upregulation of the Sur1/Trpm4 ion channel and ET-1 in the control group of mice treated with vehicle. Administration of the GLIB reduced levels of these markers in astrocytes. Additionally, cord tissues from animals treated with GLB showed increased levels of myelin basic protein and number of cells labeled for CNPase, Olig2 and PDGF-alpha indicating active remyelination activity with involvement of OPCs and mature oligodendrocytes. **Conclusion:** Astrocytic ET-1 upregulation in EAE t is significantly suppressed by treatment with GLB. Effect of GLB in associated with evidence of reduced demyelination and increased remyelination manifested as increase in CNPase, Olig-2 and PDGF-alpha.

Disclosures: T.K. Makar: None. **K. Keledjian:** None. **M.I. Ajibola:** None. **I.J. Merchenthaler:** None. **J. bryant:** None. **V. Gerzanich:** None.

Poster

PSTR358: Cellular and Molecular Mechanisms in Multiple Sclerosis and Other Demyelinating Diseases

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.29/AA11

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R35NS127253
NIH NS137233

Title: Founder haplotype analysis refines the genealogic history of the ZFHX3 repeat expansion in spinocerebellar ataxia type 4 (SCA4)

Authors: *K. FIGUEROA[1], L. HENDEN[3], M. M. GANDELMAN[2], K. WILLIAMS[3], S. M. PULST[4];
[1]Univ. of Utah, Salt Lake City, UT; [2]Neurol., Univ. of Utah, Salt Lake city, UT; [3]Macquarie Univ. Ctr. for Motor Neuron Dis. Res., Sydney, Australia; [4]Neurol., Univ. of Utah Clin. Neurosciences Ctr., SALT LAKE CITY, UT

Abstract: Spinocerebellar ataxia type 4 (SCA4) is a rare autosomal dominant neurodegenerative disorder caused by a pathogenic GGC repeat expansion in ZFHX3. Prior identity-by-state mapping suggested that the mutation arose from an ancient founder event approximately 88.5 generations, or about 2,200 years, ago; however, the rarity of SCA4 and clustering of affected families in the United States suggest that the U.S. disease chromosomes may share more recent ancestry. This exploratory genetic study used high-resolution identity-by-descent (IBD) analysis to resolve fine-scale relationships among American SCA4 families and refine the age of the SCA4 mutation. We analyzed SNP microarray data from 84 individuals from three U.S. families from Utah, Georgia, and Los Angeles. After genotype quality filtering, 117,893 SNPs were used for pairwise IBD analysis with XIBD and a European reference panel; chromosome 16 haplotypes were phased with Beagle 5.5, and the time to the most recent common ancestor (MRCA) was estimated using a likelihood-based model assuming correlated genealogy. IBD network analysis separated expansion carriers into two major clusters, one from Utah and one comprising Georgia and Los Angeles families. The clusters were connected by only two distant relative pairs sharing minimal IBD segments of less than 1 cM. Shared-segment mapping defined a 690-kb minimum overlapping interval centered on ZFHX3, within which a core 67-SNP founder haplotype was conserved across all 30 expansion carriers. Likelihood modeling estimated the MRCA at 12.4 generations (95% CI, 3.9-43.5), corresponding to approximately 310 years ago. These data support a recent U.S. founder effect for the ZFHX3 expansion rather than a solely ancient origin, helping explain the rarity and geographic clustering of SCA4. Defining this localized disease haplotype provides a framework for diagnostic haplotype

analysis, family prioritization, and development of variant-specific therapeutic strategies for SCA4.

Disclosures: K. Figueroa: None. **L. Henden:** None. **M.M. Gandelman:** None. **K. Williams:** None. **S.M. Pulst:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.01/AA12

Topic: E.05. Auditory and Vestibular Systems

Support: NSF SUSMED TRAINEESHIP
NEI R00 EY034546
Georgia Tech Smithgall-Watts Early Career Award to WP

Title: Auditory motion tracking shows a distinct two-phased behavior involving separating sound objects in space

Authors: *D. WU, W. PARK;
Psychological and Brain Sci., Georgia Inst. of Technol., Atlanta, GA

Abstract: Tracking moving objects is a vital perceptual function. While visual tracking has been extensively studied, much less is known about how humans track moving sounds. Given the differences between visual and auditory spatial processing, auditory motion tracking may rely on distinct behavioral strategies. Here, we examined human behavior in a continuous auditory pursuit paradigm.
Seventeen neurotypical young adults (4 females, 18-23 years) completed the task. Two pure tones were presented simultaneously: a self-sound controlled by the participant via a joystick (261.63Hz) and a target (493.88 Hz) that moved randomly within a simulated two-dimensional space in depth. The target direction changed at normally distributed intervals with varying means under two predictability conditions (low predictability: 3s, high predictability: 8s). Spatial locations were simulated using interaural time and level differences, and distance-related intensity cues. Participants were asked to control the self-sound to pursue and catch the target within 45 seconds.
Participants successfully caught the target on 67.13% of the trials (SD = 12.56, SEM = 3.05), with a higher success rate for the high predictability (72.21%) than the low predictability (62.06%) condition. Unlike in vision, self-target distance trajectories over time revealed a two-phase pattern in a majority of successful trials, well described by a piecewise linear regression (mean R^2: 0.5395 ± 0.3273 SD, SEM = 0.0112). During the first phase, the self-target distance counterintuitively increased over time (slope: 0.4470 ± 1.1712 SD, SEM = 0.0401), indicating that participants initially moved away from the target. During the second phase, the distance decreased rapidly until capture (slope: -1.40 ± 1.5990 SD, SEM = 0.0548). Successful trials

exhibiting this two-phase pattern ($R^2 > .3$) were completed significantly faster than those without it (Wilcoxon rank-sum $z = -14.982$, $p < .001$). Across participants, the proportion of trials exhibiting the two-phase pattern was associated with an overall higher success rate (Pearson correlation test, $r = .768$, $p < .001$), while longer average self-target distance at the phase transition was associated with an overall reduced success rate ($r = -.80$, $p < .001$).
These findings reveal a two-phase auditory tracking strategy consisting of initial separation followed by rapid pursuit. The results suggest that increasing spatial separation between sound sources may facilitate auditory object segregation before capture.

Disclosures: D. Wu: None. **W. Park:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

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Program #/Poster #: PSTR359.02/AA13

Topic: E.05. Auditory and Vestibular Systems

Support: NIH 1R15DC021563-01

Title: Comparisons of Spatial-Hearing Algorithms with Microphones Inside or Outside Ear Canals

Authors: T. HILL, A. AJAY ARUL, S. HAU, A. ZEESAN, R. MADDELA, *Y. GAI; Biomed. Engin., St. Louis Univ., Saint Louis, MO

Abstract: Head-related transfer functions (HRTFs) capture spatial properties carried by sound coming from a specific 3D location in our surroundings. They contain all major cues that are important for sound localization. In our previous studies, we developed hearing-aid algorithms that fully or partially utilize HRTF features in localizing and segregating multiple concurrent sound sources with binaural microphones. In practice, the microphones can be positioned at different locations around or inside the ears. The present study explored the effect of microphone placements on localization accuracy and speech intelligibility. In Experiment I, binaural microphones were secured to the center of outer ears on a dummy head while recording various sound profiles. Speech sound was presented via 36 loudspeakers evenly placed on a metal ring surrounding the head. Our localization and segregation algorithms were then applied to the recorded sound. In Experiment II, the dummy head was incorporated with 3D printed ears that accurately mimic the human pinnae and ear canals. The same binaural microphones were placed inside the ear canals where human eardrums are typically located. The localization model, which typically exhibits a spiral pattern at any fixed sound frequency, was compared across the two experimental conditions, showing how the microphone placements affected model performance. The speech segregation algorithm was also applied to remove unwanted sources before the processed sound was presented to normal-hearing listeners. The results provide valuable insights into the design of hardware and algorithms for intelligent spatial hearing aids.

Disclosures: T. Hill: None. **A. Ajay Arul:** None. **S. Hau:** None. **A. Zeesan:** None. **R. Maddela:** None. **Y. Gai:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

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Program #/Poster #: PSTR359.03/AA14

Topic: E.05. Auditory and Vestibular Systems

Support: NSF Grant 2319321
Brain Research Foundation Pilot Award BRFSG-2023-13
NSF Grant 2515342

Title: Distinct roles of parvalbumin and somatostatin interneurons in auditory spatial processing of complex auditory scenes

Authors: *Z. QU[1], J. NOCON[2], K. SEN[3], H. GRITTON[4];
[1]Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Univ. of Minnesota, Twin Cities, Minneapolis, MN, ; [3]Biomed. Engin., Boston Univ., Boston, MA; [4]Comparative Biosci., Univ. of Illinois, Urbana, IL

Abstract: Auditory scene analysis requires cortical circuits to preserve target-sound representations while suppressing interference from competing sound sources. Although inhibitory interneurons are well positioned to regulate this process, how distinct inhibitory cell types contribute to spatial target-masker competition remains poorly understood. Here, we used a multi-speaker auditory environment to present target sounds alone or together with spatially distributed maskers while recording auditory cortical activity in awake, passively listening mice. By combining electrophysiology, cell-type-specific optogenetic suppression, and spike-timing-based neural classifiers, we examined how parvalbumin (PV) and somatostatin (SST) interneurons contribute to spatial tuning and target discriminability in complex auditory scenes. PV and SST interneurons made dissociable, context-dependent contributions. PV suppression broadly altered spatial tuning properties, including tuning width, modulation depth, centroid, and sparseness, and reduced target discriminability under clean listening conditions. In contrast, SST suppression produced more selective effects on spatial tuning but significantly impaired neural discrimination during masked listening, weakening the improvement in target discrimination that normally accompanies increasing target-masker separation. Thus, the interneuron population that most strongly altered spatial tuning was not the one that most strongly disrupted masked target discrimination, revealing a separation between cortical mechanisms supporting spatial receptive-field structure and those supporting target-masker segregation. Together, our results suggest that PV-mediated inhibition stabilizes the fidelity of auditory cortical representations, whereas SST-mediated inhibition helps resolve competition between simultaneous sound sources, providing complementary inhibitory mechanisms for auditory scene analysis.

Disclosures: Z. Qu: None. **J. Nocon:** None. **K. Sen:** None. **H. Gritton:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.04/AA15

Topic: E.05. Auditory and Vestibular Systems

Support: NSF Grant 2319321
Brain Research Foundation Pilot Award BRFSG-2023-13
NSF Grant 2515342

Title: Spatial sound encoding in the cortex does not occur under ketamine based anesthesia

Authors: *S. P. KIM[1], Z. QU[1], H. J. GRITTON[2];
[1]Bioengineering, Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Comparative Biosci., Univ. of Illinois, Urbana, IL

Abstract: Auditory space is not represented as a simple topographic map in auditory cortex but is instead encoded through distributed patterns of cortical activity. Although auditory cortical spatial coding has been studied for decades, much of the foundational work was performed under anesthesia, leaving unclear how anesthetic state alters single-neuron and population representations of sound-source location. Here, we recorded auditory cortical single-unit spiking activity evoked by sounds from different speaker locations in the same animals during awake and ketamine/xylazine/acepromazine states. We found that ketamine-based anesthesia profoundly disrupted cortical spatial representation. At the single-neuron level, many neurons lost significant spatial preference, reflected in marked changes in spatial tuning curves, tuning width, modulation depth, and response sparseness. At the population level, trial-by-trial speaker-location representations that were clearly separable during wakefulness collapsed under anesthesia, resulting in impaired population decoding of sound-source location. This loss of spatial separability occurred despite robust sound-evoked responses: under anesthesia, cortical activity became more correlated across neurons and more strongly time-locked to the stimulus amplitude envelope. These findings indicate that ketamine/xylazine/acepromazine anesthesia does not simply suppress auditory cortical activity, but shifts the network into a correlated, stimulus-locked state that is less able to support separable spatial representations. More broadly, our results suggest that awake auditory spatial coding depends on state-dependent population dynamics that are disrupted by ketamine-based anesthesia.

Disclosures: S.P. Kim: None. **Z. Qu:** None. **H.J. Gritton:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

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Program #/Poster #: PSTR359.05/AA16

Topic: E.05. Auditory and Vestibular Systems

Support: NSF SMA-2319321
NSF EFRI-2515342
NSF 2123781
Beckman Graduate Fellowship by the Arnold and Mabel Beckman Foundation

Title: Representations of spatial saliency in auditory cortex are selectively organized through temporal coordination

Authors: *M. IRANI[1,2,3], Z. QU[4,5], K. K. SEN[7], S. SADAGHIANI[6,3,2], H. GRITTON[4,5,3,2]; [1]Univ. of Illinois, Champaign, IL; [2]Neurosci. Program, [3]Beckman Inst., [4]Comparative Biosci., [5]Bioengineering, [6]Psychology, Univ. of Illinois Urbana-Champaign, Urbana, IL; [7]Biomed. Engin., Boston Univ., Boston, MA

Abstract: Selective processing of behaviorally relevant sounds in complex environments requires dynamic modulation of auditory representations. Here, we show that behavioral salience of a sound source location selectively organizes distributed auditory cortical activity through temporal coordination rather than firing-rate modulation. Using laminar electrophysiology in behaving mice, we recorded primary auditory cortex (A1) activity during a spatial listening task in which a rewarded pure tone was consistently associated with one location while non-rewarded neutral complex sounds were presented across multiple spatial positions. Neurons showed increased response reliability, temporal precision, and spike-field coupling to gamma oscillations selectively for sounds from behaviorally relevant locations, even when those sounds were unrewarded. These effects were absent during passive listening, confirming their dependence on behavioral state. At the population level, firing rates showed heterogeneous, location-independent changes that balanced across the neural population, ruling out a rate-gain account of spatial selectivity. In contrast, gamma-coupled neurons in superficial cortical layers narrowed their spatial receptive fields and shifted their tuning centroids toward the behaviorally relevant location during task engagement. Neurons with stronger gamma coupling also exhibited sharper spatial tuning and greater trial-to-trial response reliability, directly linking the strength of temporal coordination to representational fidelity. Theta-gamma phase-amplitude coupling was further selectively enhanced for the behaviorally relevant location, suggesting that slower rhythms coordinate gamma-mediated encoding across timescales. These findings identify gamma-mediated synchronization as a candidate mechanism through which auditory cortex dynamically prioritizes encoding of behaviorally relevant spatial information, offering a solution to the challenge of selective spatial processing in the absence of topographic cortical maps.

Disclosures: M. Irani: None. **Z. Qu:** None. **K.K. Sen:** None. **S. Sadaghiani:** None. **H. Gritton:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.06/AA17

Topic: E.05. Auditory and Vestibular Systems

Support: 01DC019348

Title: Effects of Histamine on Auditory Brainstem Responses and Binaural Auditory Processing in Adult CBA/J Mice

Authors: *T. VAUGHN[1], J. A. KARA[2], C. C. LEE[3];
[1]Louisiana State Univ., Baton Rouge, LA; [2]CBS, Louisiana state university, Baton Rouge, LA;
[3]Comparative Biomed. Sci., LSU Sch. of Vet. Med., Baton Rouge, LA

Abstract: Precise auditory processing in the brainstem relies on the integration of acoustic information from both ears and is influenced by several neuromodulator systems, including the histaminergic system. Histamine can alter neuronal excitability, arousal, and sensory processing throughout the central nervous system; however, its role in binaural auditory processing remains poorly understood. In this study, we investigated the effects of systemic histamine administration on auditory brainstem responses (ABRs) during monaural and binaural stimulation in adult CBA/J mice. Animals received injections of a histaminergic agonist or saline prior to ABR testing. Responses were recorded using click and 16-kHz tone bursts presented monaurally or binaurally. Analyses focused on ABR wave amplitudes and peak latencies at suprathreshold intensities of 70- and 80-dB SPL to evaluate histamine-dependent changes in auditory neural synchrony and binaural integration. We assessed whether histamine altered central auditory processing, resulting in significant changes in ABR waveform morphology during binaural stimulation compared with monaural stimulation. These findings thus provide insight into the role of histaminergic signaling in auditory pathway function and may identify novel mechanisms underlying binaural auditory processing and sound localization.

Disclosures: T. Vaughn: None. **J.A. Kara:** None. **C.C. Lee:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.07/AA18

Topic: E.05. Auditory and Vestibular Systems

Title: Monaural Preprocessing Towards Ongoing Echo Suppression Suggests a New View of Binaural Hearing

Authors: *P. X. JORIS;
KU Leuven, Leuven, Belgium

Abstract: Reverberant sounds are omnipresent. They tax binaural hearing because echoes reach the ears from directions that differ from that of the source. Human communication relies on sustained, low-frequency energy in spaces featuring hard flat surfaces. These generate strong reverberation and scramble spatial cues but somehow do not destroy spatial perception of the source. A striking demonstration was introduced by Zurek (1980). A low-frequency continuous noise leading in one ear ("source") was mixed with a copy of the same noise but now leading from the other ear and lagging in time ("echo"). The resulting waveforms at each ear are complex in spectrum and lack consistent binaural cues pointing to one side. Nevertheless, for a range of echo delays, listeners consistently lateralize the stimulus to the side of the source. The physiological basis for this remarkable ability is unknown. Recordings from auditory nerve, trapezoid body, and lateral lemniscus were obtained in anesthetized chinchillas. Earphones were directly coupled to the ear and the axonal bundle of interest was surgically exposed to record from single axons or neurons. The main stimulus, based on Zurek's (1980), consisted of a 1-s binaural Gaussian noise delivered with an interaural time difference (ITD) leading at one ear (e.g. -0.3 ms), mixed with an echo consisting of the identical noise but opposite in ITD (e.g. +0.3 ms). The echo trailed the source with a variable delay of several (1-20) ms. ITD-sensitive neurons respond to these stimuli with a bias towards ITDs of the source. To understand this bias, a coincidence analysis was performed on responses of monaural neurons that provide input to the binaural system. Bushy cells show a bias towards the coding of time differences corresponding to the source rather than to the echo. Moreover, this bias can also be induced (or counteracted) by small intensity differences between source and echo, even though earlier work showed little effect of intensity on temporal patterns of these cells. Thus although, acoustically, ITDs associated with the source are as common as ITDs associated with the echo, neurally the former are emphasized in both monaural and binaural pathways. These results directly show the role of monaural (pre-)processing in the suppression of echoes in sustained, ongoing sounds: the spike trains fed to the binaural nuclei predominantly code ITDs of the source rather than of the echo. The results also suggest that minute differences in firing rate of a small number of neurons generate sizably lateralized percepts. Finally, they show an unexpectedly large effect of intensity on the processing of ITDs in low-frequency sounds.

Disclosures: P.X. Joris: None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

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Program #/Poster #: PSTR359.08/AA19

Topic: E.05. Auditory and Vestibular Systems

Support: NIH grant R01DC023099
NIH Grant R01DC014950
LaCroute Fellowship

Title: Binaural Fusion as a Model for Auditory Streaming Errors in the Auditory Cortex

Authors: *M. M. P. MONDESIR[1], L. A. REISS[3], S. V. DAVID[2];
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Abstract: Background: Binaural fusion is the perception of two sounds or voices as one when they reach both ears. Those experiencing hearing loss often experience abnormally broad binaural fusion and struggle to segregate voices and understand speech in noisy environments (Oh et al., 2019). Broad binaural fusion can be defined as the perception of two or more spatially separated sounds, with pitch differing by as much as 1-4 octaves, as a single object (Reiss et al., 2017). We aim to understand and treat broad binaural fusion by studying its underlying neural mechanisms. To this end, the development of an animal model is critical to acquiring this knowledge. The ferret model is appropriate due to the similarity of their auditory system to that of humans (Landemand et al. 2021) and their ability to discriminate between vowel identity and generalize over a range of voice pitches across different listening conditions (Bizley et al. 2013). **Methods**: Vowel fusion data were collected from both trained and naïve ferrets. Four synthetic vowels ("AH", "OO", "AE", "EE") at three fundamental frequencies (F0, 106 Hz, 151 Hz, and 201 Hz) were presented through loudspeakers angled +/-30 degrees in the azimuth plane. Ferrets responded to vowel stimuli via go/no-go tasks. The AE vowel was designated as the go stimulus and OO, EE, and AH vowels as no-go stimuli. Fusion was determined based on their responses to probe stimuli, consisting of dichotic vowel pairs presented from the two speakers and with same or different F0. Single unit neural data were collected from the primary auditory cortex (A1) during passive presentation of the same vowel stimuli. **Results**: Ferret behavioral responses to certain vowel pairs produced behavioral responses similar to those seen in human perceptual studies. In a previous human binaural fusion study, the dichotic pair AH-EE was perceived as the single vowel AE when presented at the same F0 (Reiss and Molis, 2021). In this study, ferrets also reported the dichotic pair AH-EE as a target, consistent with perception as AE. In contrast, the dichotic pair AH-OO was treated as a no-go stimulus. The collected electrophysiology data further supports this evidence for fusion, as preliminary population response analysis shows that neural responses to the dichotic pair AH-EE are similar to responses to the single vowel AE in trained ferrets. **Conclusions**: Ferrets can reliably discriminate between vowels in go/no-go behavior, and responses to probe vowel pairs are consistent with human fusion percepts. Single unit activity in A1 shows responses consistent with the fusion percept.

Disclosures: M.M.P. Mondesir: None. **L.A. Reiss:** None. **S.V. David:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

Location: WCC Halls A-C

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Program #/Poster #: PSTR359.09/AA20

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC007690
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Title: Frequency-Space Relationships in Barn Owl Auditory Pathways: Comparing Identity and Spatial Processing Streams

Authors: *R. FERGER, J. L. PENA;
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Abstract: Previous work in barn owl midbrain has revealed a systematic relationship between frequency tuning and spatial representation in the space map: neurons representing frontal space preferentially respond to higher frequencies than neurons representing peripheral space. This frequency-space correlation emerges within the topographic space map of ICx, where precise spatial representations are first established. However, the barn owl auditory system employs two parallel forebrain pathways: an identity pathway (ICCcore, Ov, Field L) that bypasses spatial maps entirely, and a precise localization pathway (ICCcore, ICCls, ICx, OT, nRt, Entopallium). Whether frequency-space relationships are pathway-specific has implications for the functional organization of auditory processing.
We recorded spiking activity in both pathways (Field L, nRt) of anesthetized barn owls while presenting auditory stimuli via earphones corresponding to multiple azimuthal locations by varying the interaural time difference (ITD). For each recorded unit, we quantify frequency tuning (0.5-12 kHz) and spatial receptive fields, then analyze correlations between best frequency and preferred azimuth. Dimensionality reduction methods for population-level analyses examined whether alternative organizational principles emerge in each pathway.
As predicted, Field L exhibits robust frequency tuning but lacks the systematic frequency-space correlations observed in midbrain space maps. This absence supports the hypothesis that frequency-space relationships emerge specifically in the midbrain space maps. However, data from nRt, which is expected to inherit the frequency-space relationship, so far does not show this on a single unit or population level. This suggests that a reorganization takes place between midbrain and forebrain, possibly matching coding schemes found in mammalian brains.

Disclosures: R. Ferger: None. **J.L. Pena:** None.

Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH RO1 DC00788

Title: Non-hebbian synaptic plasticity at excitatory synapses onto neurons of the medial superior olive during early post-hearing development

Authors: R. GAO, L. L. SCOTT, M. T. HARNETT, *N. L. GOLDING;
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Abstract: Animals need to continuously adapt to changes in sensory cues within the environment during development. For example, sound localization neurons in the medial superior olive (MSO) undergo substantial changes in morphology and channel compositions to optimize their firing patterns tuned to interaural time differences. Previous computational studies have modeled this change with spike-time dependent plasticity (STDP), which adjusts synaptic weights based on the temporal coincidence of excitatory postsynaptic potentials (EPSPs) and action potentials. However, the high firing rates of MSO neurons create phase ambiguity in the sequence of EPSPs and action potentials that conventional STDP models cannot interpret. Moreover, recordings have shown that action potentials attenuate strongly as they propagate into the distal dendrites of MSO neurons, limiting their ability to influence synaptic integration in these distal regions. To investigate cellular learning rules underlying synaptic plasticity in MSO neurons, we made whole-cell patch recordings from MSO neurons in slices prepared from Mongolian gerbils of either sex shortly after hearing onset (P15-P20; recordings at 35°C). We monitored pharmacologically isolated EPSPs (1μM strychnine) at 0.1Hz before and after plasticity induction stimuli. Induction stimuli consisted of trains of EPSPs paired with coincident subthreshold or suprathreshold current injections, and were applied 3 times at 100Hz for 1 second, with 30-second intervals. Surprisingly, we observed long-term potentiation (LTP) of synaptic responses after both subthreshold and suprathreshold inductions (subthreshold: 35.6±13.8% increase in EPSP amplitude, n=7; suprathreshold: 41.0±45.7% increase in EPSP amplitude, n=6). No significant difference was observed in LTP induced with subthreshold and suprathreshold induction stimuli (p=0.77), indicating that action potentials are not strictly necessary for LTP in MSO neurons. The magnitude of LTP induced by subthreshold induction trains was strongly attenuated when MSO neurons were recorded with pipettes containing of the fast calcium chelator BAPTA (13.3±5.1%, n=3, 10nM), indicating a critical contribution of postsynaptic calcium within the dendrites. Our data reveal that LTP in excitatory inputs to MSO neurons is governed by non-Hebbian, action potential independent mechanisms. Our results highlight the potential for important roles of local dendritic sources of calcium influx, such as NMDA and calcium-permeable AMPA receptors, during early post-hearing development.

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Poster

PSTR359: Auditory Processing: Sound Localization and Binaural Interactions

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC011499
NIH Grant DC020459

Title: Active sensorimotor strategies for sound localization in complex acoustic scenes

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Abstract: Survival depends on rapidly detecting salient sounds (e.g., predators or food) and estimating their location to direct appropriate behavioral responses (e.g., escape or approach). In complex environments, multiple sounds may overlap in their acoustic features and compete for attention, making localization more challenging. To resolve spatial ambiguity, animals naturally sample their environment with head- and body-orienting movements, thereby converting static binaural and level cues into signals that vary in time with self-motion. While active sensing strategies are ubiquitous in nature, laboratory sound localization studies typically restrict head movement during stimulus presentation, which fundamentally alters auditory spatial perception and neural activity.

To investigate the behavioral strategies that support naturalistic sound localization, we developed a freely moving auditory discrimination task. We trained C57BL/6J and CBA/CaJ mice to localize a target sound along the perimeter of an open, circular arena while ignoring a distractor presented simultaneously from another position. After trial initiation, both stimuli (0.5 octave noise bands) played continuously until mice approached and licked a water spout under the perceived target location. To observe how acoustic complexity affects localization behavior, we varied the spatial and spectral separation between the target and distractor.

Over several weeks of training, mice adopted a variety of sensorimotor strategies that facilitated task learning, including head and body scanning movements at stimulus onset and reorienting turns to correct errant approaches toward the distractor. Mice learned to deploy these kinematic strategies according to trial difficulty, resulting in improved discrimination between spatially and spectrally ambiguous stimuli. This behavioral flexibility demonstrates that mice resolve perceptual ambiguity with active sensing strategies and update motor plans continuously in response to ongoing acoustic input.

Auditory cortex (ACtx), which mediates frequency discrimination and learned stimulus associations, could guide target localization in this task. However, ACtx lacks an organized spatial map, leaving its contribution to sound-guided orienting behavior unclear. To understand its role in active sound localization, we are currently inactivating ACtx in mice performing this freely moving discrimination task. Results of our ongoing work will identify candidate neural circuits underlying the dynamic sensorimotor transformations that support naturalistic sound localization.

Disclosures: R.M. Cassidy: None. **R.S. Williamson:** None.

Poster

PSTR360: Vestibular Processing and Perception

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Topic: E.05. Auditory and Vestibular Systems

Support: R01DC002390
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Kavli Neuroscience Discovery Institute Distinguished Postdoctoral Fellowship

Title: Biomimetic vestibular prosthesis improves neck muscle coordination and head stability during locomotion

Authors: *R. WEI[1], O. R. STANLEY[2], K. E. CULLEN[3];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Biomed. Engin., Johns Hopkins University, Dept. of Biomed. Engin., Baltimore, MD; [3]Dept. of Biomed. Engin., The Johns Hopkins Univ., Baltimore, MD

Abstract: The vestibulospinal system is critical for postural control and head stabilization during locomotion. Patients with bilateral vestibular dysfunction experience debilitating gaze instability and balance impairments. The vestibulo-collic reflex, which drives neck muscle responses to head motion, is critical for maintaining head stability. Building on our prior work showing that gait-phase-dependent neck muscle recruitment enables effective head stabilization in intact monkeys, we investigated how vestibular signals support head stability and whether head-motion-driven vestibular prosthetic stimulation can restore function. We recorded intramuscular EMG from splenius capitis and sternocleidomastoid muscles in monkeys with complete bilateral vestibular loss (BVL), with and without vestibular prosthetic stimulation during overground and treadmill locomotion across speeds. Head and body motion were captured using an inertial sensor and optical tracking, while limb motion was extracted from high-speed video using DeepLabCut. Principal component analysis quantified population-level muscle coordination. After bilateral vestibular ablation, monkeys displayed large head oscillations and insufficient compensation for trunk motion, accompanied by diminished phase dependence of neck muscle activity. Muscle coordination was also less consistent across walking speeds, although overground locomotion remained distinct from speed-matched treadmill walking. Among tested prosthetic strategies, biomimetic stimulation with irregular, motion-dependent pulse timing produced the greatest improvement in head stability. Following baseline testing, animals performed treadmill walking with stimulation. Head motion progressively stabilized across the adaptation period, and these improvements partially persisted during subsequent washout trials after stimulation was turned off. Post-adaptation, head kinematics became more stable, and gait-phase-dependent muscle modulation was largely restored. Population muscle coordination also recovered a more structured activation pattern across treadmill speeds, while overground walking continued to elicit distinct activation patterns. These findings highlight that vestibular inputs are critical for coordinating neck muscle activity and stabilizing the head during locomotion. Biomimetic vestibular prosthetic stimulation provides functionally relevant feedback that can be used during naturalistic behavior. These insights may inform future therapeutic approaches for vestibular disorders by enhancing strategies to restore functional locomotion in affected populations.

Disclosures: R. Wei: None. **O.R. Stanley:** None. **K.E. Cullen:** None.

Poster

PSTR360: Vestibular Processing and Perception

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Topic: E.05. Auditory and Vestibular Systems

Support: National Aeronautics and Space Administration contract No. 80NSSC21C0253
National Science Foundation Graduate Research Fellowship

Title: Validated Model of Galvanic Vestibular Stimulation Modulating Spatial Orientation Perception

Authors: *C. R. AUSTIN, A. R. ALLRED, T. K. CLARK;
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Abstract: Galvanic Vestibular Stimulation (GVS) is a method for altering vestibular-mediated processes such as balance, motion sickness, and perception, via low-level electrical stimulation delivered via electrodes typically placed on the mastoids. There is increasing interest in using GVS as a clinical, scientific, and operational tool, which drives the need for quantification and prediction of GVS's effects on spatial orientation perception. Here we leverage experimental perceptual reports from both bi-polar GVS (an electrode is placed on each mastoid behind each ear with opposite current polarity, producing primarily roll tilt perceptions) and co-polar GVS (electrode(s) are added distally with the mastoid electrodes now having the same polarity, producing primarily pitch tilt perceptions). Both data sets were used to tune and validate a modified observer model framework (Clark et al., 2015b, 2015a; Merfeld et al., 1993) in order to predict self-tilt perceptual responses from omni-polar GVS (combination of bi-polar and co-polar in which the mastoid electrode current can vary independently). To quantify GVS perceptual effects, participants used a subjective haptic horizontal reporting task while experiencing different combinations of GVS and physical tilt motion in either a roll tilt plus bipolar GVS (n=11) or pitch tilt plus co-polar GVS (n=20) paradigm. An observer model of vestibular-driven perception was modified to include pathways to capture effects of bipolar GVS, accounting for transfer function dynamics and asymmetries observed in semicircular canal sensory response to GVS (Forbes et al., 2023; Kwan et al., 2019), as described in (Allred et al., 2024). This initial model was sensitive to the small, but significant changes in tilt perception induced by the co-polar stimulus. However, to correct the direction of co-polar predictions, we applied an additional gain parameter to the posterior canal along the GVS pathways as proposed by (Day et al., 2011). Fitting this posterior canal gain using a subset of the co-polar data set yielded a gain value of 1.35. Additionally, introducing the posterior canal gain reduced the mean squared error between the model predictions and bipolar validation data set, improving the model's ability to predict bipolar responses. Together, these results indicate that the inferior vestibular nerve (innervating the posterior canal) is likely preferentially stimulated by GVS. Further, our resultant model was able to predict tilt perceptual responses to arbitrary combinations of physical motion

and omni-polar GVS stimuli, enhancing model-based capabilities for altering vestibular-mediated processes.

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Poster

PSTR360: Vestibular Processing and Perception

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.04/AA26

Topic: E.05. Auditory and Vestibular Systems

Title: Cross axial interactions in sequential versus simultaneous horizontal and vertical VOR adaptation

Authors: *I. O. SPEIRS, T. L. STAY;
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Abstract: The vestibulo-ocular reflex (VOR) stabilizes vision during head rotation. VOR responses work in tandem across different axes, using information from all the canals and otolith organs (Angelaki et al., J Neurophys, 2002), but it is not clear how broadly adaptation in one axis, which presumably uses a subset of canal input, generalizes to affect responses in a separate axis. We explore the difference in this degree of generalization in sequential versus simultaneous horizontal and vertical VOR adaptations. These findings could help inform about synaptic mechanisms for vestibular adaptation, such as whether resources for synaptic plasticity are shared or strictly compartmentalized by axis of rotation. We performed repeated measures gain-down training in mice (C57BL/6J, n experiments=11, n mice=6) of both sexes, all younger than eight months. Mice were head-fixed to a rotating platform surrounded by a drum rotating in phase at the same frequency (0.5 Hz, 31 deg/sec peak velocity). Eye movement was tracked with video oculography. Horizontal training (H) occurred around the earth-vertical axis, vertical

training (V) occurred around the earth-horizontal axis, and simultaneous training was a cross-axial mix of equal peak velocity (C). Training consisted of three variations, each with two, thirty-minute sessions: H then V, V then H, and C twice. As expected, the preliminary sequential training showed a marked reduction in the cross-axial reflex after both individual axes were trained (-42.16% ± 20.14). For the simultaneous training paradigm, a larger, less variable decrease in the cross-axial reflex was seen after both training sessions (-63.48% ± 3.88). This pattern suggests a smaller amount of generalization across axes in the sequential paradigms compared to the combined paradigm. We hypothesize that this may be driven by depleted synaptic resources in a shared pool, where the training of the first axis reduces available resources for the adaptation of the second axis. We are continuing to collect data to resolve these general trajectories and offer insights into the underlying molecular mechanisms.

Disclosures: I.O. Speirs: None. **T.L. Stay:** None.

Poster

PSTR360: Vestibular Processing and Perception

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Title: Unilateral superior canal dehiscence syndrome alters head kinematics during gaze stabilization tasks

Authors: *R. ARYAN[1], J. L. MILLAR[2], J. P. CAREY[3], M. C. SCHUBERT[3], K. E. CULLEN[1]; [1]Dept. of Biomed. Engin., [2]Physical Med. and Rehabil., [3]Otolaryngology-Head and Neck Surgery, Sch. of Medicine, The Johns Hopkins Univ., Baltimore, MD

Abstract: Introduction: Superior canal dehiscence syndrome (SCDS) occurs when a pathological opening forms in the bone over the superior semicircular canal, leading to abnormal vestibular stimulation. Although patients experience vestibular and auditory symptoms, the impact of this condition on head movements is not fully understood. Therefore, we examined how unilateral SCDS affects head movements during six gaze stabilization tasks, and whether

head kinematics in unilateral SCDS are associated with clinical measures. **Methods:** 15 patients with unilateral SCDS (age=45y; based on Barany Society criteria) and 15 controls (age=46y) performed 3 horizontal and 3 vertical gaze stabilization tasks. 3D rotational velocities and linear accelerations were recorded using a head-mounted IMU. Signal range, standard deviation, variability, asymmetry, head angular displacement range, and temporal measures of head rotation were compared between groups. **Results:** Group differences were most prominent during horizontal tasks: roll velocity range was significantly lower in patients than controls across all 3 horizontal tasks, with the strongest difference observed for the far earth-fixed target ($p<0.01$). Roll displacement range was reduced in patients during horizontal tasks using near earth-fixed or handheld targets ($p<0.05$); unilateral SCDS also showed a higher CV of head cycle duration during these tasks ($p<0.05$). In vertical tasks, the only significant group difference was patients' greater yaw velocity asymmetry observed for the far earth-fixed target ($p<0.05$). Across both task categories, kinematic measures correlated more frequently with functional and perceived clinical measures than with vestibular physiological measures. In all horizontal tasks, greater roll displacement variability correlated with poorer upward visual acuity, PPPD symptoms, and dizziness handicap inventory scores ($p<0.05$). In vertical tasks, higher ipsilesional horizontal visual acuity was correlated with greater yaw velocity range in all tasks and with greater pitch velocity range and shorter cycle duration in 2 of 3 tasks ($p<0.05$). **Conclusions:** Head kinematics differ between unilateral SCDS patients and healthy controls, mainly during horizontal head rotations. Lower roll displacement variability during horizontal rotations was associated with better upward visual acuity and lower dizziness symptom burden, whereas greater yaw and pitch velocity ranges during vertical rotations were associated with better ipsilesional visual acuity. Wearable head kinematics during gaze stabilization tasks may provide objective markers of functional impairment in unilateral SCDS.

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Poster

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Program #/Poster #: PSTR360.06/AA28

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant 90111734

Title: Galvanic vestibular stimulation is transformed in central vestibular pathways for posture and perception

Authors: *B. A. RAMADAN[1], C. BAO[3], L. J. GÓMEZ[4], K. E. CULLEN[2];
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Abstract: Galvanic vestibular stimulation (GVS) provides a non-invasive approach to modulating vestibular reflexes and perception in humans. Experimental studies have shown that GVS can evoke eye movements, alter postural sway, and influence self-motion perception. Importantly, GVS is also increasingly used clinically to improve postural recovery following balance perturbations in individuals with peripheral vestibular impairment. However, despite its broad experimental and clinical use, little is known about how GVS is encoded by central vestibular neurons at the single-unit level. Previous neurophysiological studies in rhesus monkeys have shown that regular and irregular vestibular afferents encode GVS differently from physical whole-body motion, with less high-pass response dynamics across equivalent stimulus frequencies (Kwan et al., 2019). Here, we asked how GVS is represented in central vestibular pathways for posture and perception. Vestibular-only (VO) neurons in the vestibular nuclei (VN) provide the key link between vestibular afferents and descending vestibulospinal pathways involved in posture, while also providing ascending input to ventral posterolateral thalamus (VPL). VPL, in turn, relays vestibular signals to cortical pathways implicated in self-motion perception. We therefore recorded single-unit activity from VO neurons in VN and neurons in VPL using Neuropixels probes in head-fixed *Macaca mulatta*. Stimulation parameters included binaural, suprathreshold sinusoidal GVS from 0.1 to 25 Hz at ±1 mA. Because irregular vestibular afferents provide the primary input to VO neurons, we used previously reported irregular afferent responses as the peripheral reference for evaluating central transformation. This comparison revealed that GVS response dynamics are reshaped across central processing stages. Although VO neurons in VN showed lower overall gains than irregular afferents during sinusoidal GVS, gain increased with frequency in both populations, with a steeper slope in VN (Bode magnitude increase rate 0.14 vs. 0.39 dB/decade). In VPL, this high-pass tuning was further enhanced (0.42 dB/decade). Response phase was also altered: VN neurons showed increasing phase leads at high frequencies, reaching 107° at 25 Hz compared with 49° in irregular afferents, whereas VPL neurons displayed a broad distribution of response phases, with an average near 0° at 25 Hz. Together, these findings show that GVS encoding is transformed across VO neurons and VPL, providing insight into how galvanic stimulation engages central pathways involved in posture and self-motion perception.

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Poster

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Topic: E.05. Auditory and Vestibular Systems

Support: ASFOR Grant FA9550-24-1-0300 DEF

Title: Decoding vestibular illusion from neural population dynamics

Authors: *J. CARRIOT, I. MACKROUS, M. J. CHACRON;
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Abstract: Spatial disorientation remains a major threat to flight safety when visual cues are sparse or unreliable. A prominent example is the somatogravic illusion, in which sustained linear acceleration, such as during take-off, is misinterpreted as a nose-up pitch tilt. This perceptual failure reflects the vestibular system's tilt-translation ambiguity: otolith afferents encode the net gravito-inertial force and therefore cannot, on their own, distinguish inertial acceleration from changes in head orientation relative to gravity. While single-neuron responses can reveal candidate correlates of this illusion, the computations that transform ambiguous vestibular signals into a coherent but erroneous percept are likely distributed across neural populations. Here, we examine population activity recorded from central vestibular neurons in behaving non-human primates exposed to motion stimuli designed to dissociate translation, tilt, and illusion-inducing gravito-inertial contexts. Using population-level analyses, including neural state-space trajectories and decoding approaches, we ask whether vestibular illusions are associated with a distinct population state rather than a simple amplification of responses to linear acceleration. Preliminary results suggest that illusion-inducing stimuli drive coordinated changes in population activity that separate them from physically similar translation conditions and evolve in register with the animals' perceptual reports. These findings support the idea that vestibular illusions emerge from population-level dynamics that resolve ambiguous otolith signals into an internal estimate of self-motion and orientation. More broadly, this work provides a framework for identifying neural signatures of spatial disorientation and for developing future strategies to predict or mitigate vestibular illusions during flight.

Disclosures: J. Carriot: None. **I. Mackrous:** None. **M.J. Chacron:** None.

Poster

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Topic: E.05. Auditory and Vestibular Systems

Support: CIHR

Title: Beyond the hypothesis: Modeling stochastic resonance during noisy vestibular stimulation

Authors: *I. MACKROUS[1], J. CARRIOT[2], K. E. CULLEN[3], M. J. CHACRON[1];
[2]Physiol., [1]McGill Univ., Montreal, QC, Canada; [3]Dept. of Biomed. Engin., The Johns Hopkins Univ., Baltimore, MD

Abstract: Galvanic vestibular stimulation (GVS) is a non-invasive technique that modulates vestibular afferent activity through the application of weak electrical currents delivered across the mastoid processes. Owing to its safety, ease of use, and therapeutic potential, GVS has gained increasing attention as a tool to probe vestibular function and improve balance. In

particular, several studies have reported that subthreshold noisy GVS (nGVS) improves behavioral performance in both healthy individuals and patients with vestibular disorders, resulting in reduced postural sway and enhanced balance control. The mechanisms underlying these behavioral benefits remain poorly understood. A leading hypothesis is that nGVS acts through stochastic resonance, a phenomenon whereby the addition of an optimal level of noise enhances the detection and transmission of weak signals in nonlinear systems. In threshold-based systems, stochastic resonance predicts that noise can improve signal encoding by facilitating threshold crossings that would not otherwise occur, thereby increasing signal fidelity. This framework has been widely invoked to explain the beneficial effects of nGVS on behavior. Despite its popularity, direct evidence supporting stochastic resonance as the neural mechanism underlying nGVS remains largely absent. Moreover, classical stochastic resonance theory was developed for systems with little or no intrinsic noise. Whether the same principles apply to neurons, which operate in the presence of substantial intrinsic variability arising from synaptic and membrane fluctuations, remains unclear. To address this question, we developed leaky integrate-and-fire (LIF) models constrained by the physiological properties of 83 vestibular-only (VO) neurons recorded in the vestibular nuclei. For each neuron, we quantified the effects of nGVS on the encoding of vestibular stimuli across a range of operating regimes and noise amplitudes. Preliminary results indicate that stochastic resonance induced by nGVS is a plausible neural mechanism, but that its emergence strongly depends on the operating regime of individual neurons. These findings provide mechanistic support for the hypothesis that stochastic resonance contributes to the behavioral improvements observed with nGVS and highlight the importance of neuronal state in determining its effectiveness. More broadly, this work establishes a computational framework for identifying optimized nGVS parameters that may maximize sensory encoding and improve behavioral outcomes.

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Poster

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Program #/Poster #: PSTR360.09/AA31

Topic: E.05. Auditory and Vestibular Systems

Support: b

Title: Defining contributions of the vestibular nuclear complex (VNC) to vestibular short latency evoked potentials (VsEPs) and motor performance

Authors: *D. NAQVI[1,2], R. D. BRAUN[1,2], M. NIWA[1], A. HOLT[1,2];
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Abstract: The vestibular system is crucial for posture, gait, and the perception of head and body position in space. Our lab has shown that linear jerk stimulation of irregular vestibular afferents

preferentially activates central vestibular pathways and is measurable with vestibular short-latency evoked potentials (VsEPs). Lesion studies in chickens show that VsEP P2 and later peaks reflect central pathway activity (Nazareth & Jones, 1997). However, the origin of mammalian VsEP P2 and later peaks remains unclear. Inhibitory designer receptors exclusively activated by designer drugs - DREADDs (synthetic receptors that modulate neuronal activity once bound) were used to determine 1) vestibular nuclear complex (VNC) contributions to late VsEP peak(s) and 2) the effect of dampening neuronal function on motor performance.The effect of inhibitory DREADD expression was tested across the rostro-caudal extent of the VNC in adult rats (rostral (ROS), n=7; mid rostro-caudal (MRC), n=4). Four weeks after stereotaxic delivery, each rat was tested in three VsEPs experiments (4,000 naso-occipital jerks) separated by at least one week. Before administering deschloroclozapine (DCZ; DREADD agonist), saline was administered to compare VsEPs before and after DCZ. Experiments were designed to control for the potential effect of repeated stimulation and habituation (saline only, constant, or varied jerk intensity). Latency to fall was assessed in the MRC group while walking on an accelerating rotarod (5-48 rpm) following saline/DCZ under light and dark conditions. Expression was assessed after transcardial perfusion, postfixation, cryoprotection, sectioning, and imaging of the brain.The ROS group had significantly reduced P3 amplitude and increased P2 latency after DCZ compared to saline using a constant jerk intensity ($p<0.05$). Saline administration did not affect VsEP ($p>0.05$). With increasing jerk intensities, P1-3 amplitudes increased and latencies decreased after both treatments. Across jerk intensities, DCZ reduced P3 amplitude and increased P2 and P3 latencies. Unlike the ROS group, only P2 latency increased after DCZ in the MRC group, trending towards shorter rotarod latencies in light ($p=0.104$) and dark ($p=0.057$).Our data demonstrate that central pathways contribute to the late peaks of the mammalian VsEP (P2/P3). Spatial differences in the contributions to VsEP late peaks, may reflect unique distributions of irregular fibers across the VNC. These fibers in the MRC VNC may also contribute to vestibular related motor function. Future work should determine how ROS VNC inhibition relates to motor performance and whether VsEP changes predict behavioral deficits.

Disclosures: D. Naqvi: None. **R.D. Braun:** None. **M. Niwa:** None. **A. Holt:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.01/AA32

Topic: E.06. Vision

Support: NIH Grant R01EY026286

Title: Comprehensive characterization of functional cell types in the mouse superficial superior colliculus

Authors: *C. LAGAS[1], J. REN[1], H. CHEN[2], J. CANG[1];
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Abstract: A major and highly conserved component of the mammalian visual system is the superior colliculus. This multi-layered subcortical structure receives direct retinal projections into the superficial layer, of which is primarily involved in visual motion processing. The composition of the superficial superior colliculus (sSC) has been defined into different neuronal subtypes, based on morphology, spatial organization, visual responses, or molecular expression. For example, a recent study from our lab identified 28 molecularly distinct neuronal subtypes in the sSC (*Liu et al.,* 2023, PMID: 37086721), revealing previously unrecognized functional complexity of the sSC. Although studies have worked to define functional characteristics of the sSC, whether clear functional cell types exist are not well defined, especially with how they may be related to motion processing and molecularly defined cell types. The current study aims at uncovering these sSC functional cell types through a comprehensive stimulus presentation, with a particular focus on motion stimuli. To address this, we used two-photon calcium imaging with simultaneous stimulus presentation to the contralateral eye. We measured sSC neuronal responses to different visual stimuli, including over 700 distinct visual conditions assessing parameters such as direction, size, speed, luminance, and contrast. Preliminary data utilizing an ecologically relevant visual stimulus called "flow" (*Dyballa et al*., 2018, PMID: 30327345) demonstrates a wide range of responses to different conditions, and functional clustering based on these parameters emerges. Cells in the sSC also demonstrate varying levels of selectivity to different parameters, which could be used to further investigate differences between clusters like selectivity for direction or responsiveness to speeds. This study more thoroughly defines the functional characteristics of the sSC neurons into cell types and will provide insight into the role of molecular identities in visual processing.

Disclosures: C. Lagas: None. **J. Ren:** None. **H. Chen:** None. **J. Cang:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.02/BB1

Topic: E.06. Vision

Support: NIH Grant R01EY026286

Title: Computation of visual motion variables in the mouse superior colliculus

Authors: *J. REN[1], J. LIU[2], H. CHEN[2], J. CANG[2];
[1]Biol., Univ. of Virginia, CHARLOTTESVILLE, VA; [2]Univ. of Virginia, Charlottesville, VA

Abstract: Motion processing is a crucial function of the visual system, which requires extracting the global direction and true speed of moving objects invariant to local spatial features. This computation is classically attributed to higher visual cortical areas, such as the primate MT.

However, the subcortical structure superior colliculus (SC) is known to drive innate visually guided behaviors such as capturing fast-moving prey and escaping from looming predators. These behaviors also demand reliable visual motion computation, but whether and how the SC encodes the global direction and true speed remains largely unclear. In this study, we used Neuropixels ultra-high density (UHD) probes to record from the SC of awake head-fixed mice. We presented a boids-inspired "flow" stimulus and systematically varied its direction, speed, size of the flow dots, and local directional variability. SC neurons displayed robust and diverse responses and motion selectivity to this stimulus. At the single-cell level, about half of the motion selective SC neurons showed speed tuning that was consistent across flow-dot size. Notably, the proportion of these ”true“ speed neurons was slightly higher in deeper layers. On the other hand, direction-selective neurons invariant to local directional variability were enriched in more superficial layers of the SC. Across the population, speed and direction coding were independent, and distributed continuously along the feature axes. Next, we trained linear decoders on SC population responses to decode motion speed and temporal frequency. Within the SC, the cross-condition generalization performance for speed significantly exceeded that for temporal frequency. Crucially, the SC's speed-decoding performance consistently surpassed the benchmark performance of both retinal and cortical responses generated by established “digital twin” models. Furthermore, analysis of the response temporal dynamics revealed that speed representations emerged later than direction in the SC. Together, these results indicate that the SC does not passively relay retinal signals. Instead, it performs high-level feature abstraction, extracting invariant speed and direction through independent and asynchronous computations.

Disclosures: J. Ren: None. **J. Liu:** None. **H. Chen:** None. **J. Cang:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.03/BB2

Topic: E.06. Vision

Support: NIH EY026286

Title: Influence of single-neuron optogenetic perturbations in the mouse superior colliculus

Authors: *V. DEPIERO[1], H. CHEN[2], S. TANABE[3], B. SCHOLL[5], J. CANG[4];
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Abstract: The superior colliculus (SC) or optic tectum in non-mammalian species is a well-established hub for processing of visual motion information. In the mouse visual system, direction-selective ganglion cells (DSGCs) project and synapse onto neurons in the superficial layer of the SC (sSC). Transformation of retinal motion information to collicular responses shows a direct relay of direction selectivity. How those visual signals are processed locally in the

sSC remain unclear. We aim to explore the influence of local DS neurons within the sSC using two-photon imaging and simultaneous targeted optogenetic stimulation.
Our all-optical approach consists of co-expressing the soma targeted, red-shifted opsin, ChRmine, and GCaMP6 in either excitatory or inhibitory neurons of the sSC. This experimental paradigm allows us to record visual responses to drifting gratings of different directions while optogenetically activating target sSC neurons. We can measure the influence targeted neurons have on neighboring sSC neurons to help establish functional connectivity rules within the colliculus. Studies using all optical approaches in mouse V1 have established several local connectivity and functional interactions related to processing of visual features. Given the predominance of inhibitory neurons in the sSC, our experiments will likely reveal novel neural circuitry and visual computation in the sSC.

Disclosures: V. DePiero: None. **H. Chen:** None. **S. Tanabe:** None. **B. Scholl:** None. **J. Cang:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

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Program #/Poster #: PSTR361.04/BB3

Topic: E.06. Vision

Support: NIH Grant R01EY026286
NIH-NINDS U01NS122040

Title: Morphological characterization of genetically defined cell types in the mouse superior colliculus

Authors: *D. EAVES[1], C. CHEN[2], A. KIPCAK[2], J. CANG[1], A. ERISIR[2];
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Abstract: The superior colliculus (SC) is a midbrain structure organized both retinotopically along the surface and into distinct layers characterized by their anatomy, inputs, and outputs. Previous work in the superficial SC (sSC) has identified neuron types using molecular markers, function, and morphology. Additionally, transgenic mouse lines have facilitated access to genetic cell types, enabling reliable labeling and manipulation of cell subtypes. In this study, we aim to use Cre-dependent fluorescent reporters and high-resolution confocal Z-stacks to reconstruct neurons and their dendrites in the GRP-KH288-Cre, Cbln4-IRES-Cre, and VIP-IRES-Cre mouse lines. We evaluated dendritic field extent and orientation of cells (n=46), as well as soma size and shape using 3D soma measurements (n=389) of volume, sphericity, and oblate ellipticity. The GRP mouse line visualizes dorsoventrally oriented fusiform cells that have significantly larger somas ($p<0.01$) and are located more ventrally than cells in other lines. These display bipolar dendrites, consistent with Narrow Field classification. VIP+ neurons are located more dorsally relative to GRP cells, and their somas are more spherical than other lines (median

sphericity index=0.818, $p<0.05$). The dendrites of VIP+ cells spread in all dimensions (convex hull median=0.653, vs. other lines, $p<0.05$), consistent with multipolar morphology attributed to Stellate cells. In the Cbln4 line, multiple cell morphologies are visualized, identifiable by their soma volume, distance to the surface, and sphericity. Most Cbln4 neurons display fusiform somas oriented horizontally (n=84/149), with two primary dendrites extending laterally, consistent with Horizontal cell classification. A second subtype is significantly larger ($p<0.01$) and located closer to the surface of the SC (median=0 microns, $p<0.01$). This population may reflect a subpopulation (n=43/149) consistent with Marginal cell morphology. In summary, the GRP and VIP mouse lines allow access to uniform populations of Narrow Field and Stellate cells, although it cannot be confirmed if all sSC cells with Narrow Field or Stellate morphology express GRP or VIP respectively. On the other hand, the Cbln4 line provides access to two morphologically distinct populations. This work provides foundational knowledge for future manipulation of neuron subtypes using intersectional genetic and functional approaches.

Disclosures: D. Eaves: None. **C. Chen:** None. **A. Kipcak:** None. **J. Cang:** None. **A. Erisir:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

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Program #/Poster #: PSTR361.05/BB4

Topic: E.06. Vision

Support: U01NS136405
R01EY030138
RPB-Stein Award
GRF-CFC3

Title: TransA-MERFISH decodes retinotectal circuits by integrating anterograde trans-synaptic tracer with spatial transcriptomics

Authors: *C. LIU[1], L. ZHANG[1], F. WANG[1], X. GE[1], N. Y. TSAI[1], S. CHANG[1], Y. WANG[1], K. NIMKAR[2], S. KANG[1], P. LIN[1], S. YAO[3], K. SHEKHAR[2], M. SCANZIANI[1], E. H. FEINBERG[1], X. DUAN[1];
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Abstract: One of the major goals in modern neuroscience is to construct such comprehensive atlases. While significant advances have been made in mapping neural circuits across brain regions, cell types, and synapses, fully uncovering a circuit's connections and information flow remains difficult. Our previous toolkit, “Trans-Seq,” integrates a redesigned anterograde trans-neuronal tracer, mWGA-mCherry (mWmC), with single-cell RNA sequencing (scRNA-seq) to identify postsynaptic partners from genetically or regionally specified starter neurons in a high-

throughput way. Nonetheless, enzymatic dissociation of target regions in preparing scRNA-seq samples leads to low neuronal recovery and loss of spatial context. To address these challenges, we developed a scalable technology for mapping mammalian brain circuits that integrates Multiplexed Error-Robust Fluorescence In Situ Hybridization (MERFISH) with anterograde trans-neuronal tracing (TransA-MERFISH). TransA-MERFISH significantly increases neuron capture rates in the adult brain while preserving the spatial distribution of individual neurons. To begin, we used TransA-MERFISH to map connectivity from retinal ganglion cells (RGCs) to retinorecipient neurons in superior colliculus (SC). We first optimized the MERFISH protocol to enable simultaneous detection of mWmC and multiplexed RNA transcripts. We then investigated retinotectal circuits to comprehensively map connectivity from alpha-RGCs (αRGCs) to all their retino-recipient neurons in SC. This recovered four excitatory neuronal types as αRGC recipients, among a total of eight excitatory neuronal clusters in the retino-recipient zone (superficial SC, sSC), including the previously validated Nephronectin-positive (Npnt+) wide-field neurons. In addition, four inhibitory neuronal types were characterized among the ten inhibitory clusters in sSC, including a specific Somatostatin+ (Sst+) SC neuron cluster that receives αRGC inputs. To functionally decode these parallel retinotectal circuits, we recorded *in vivo* calcium activity in post-synaptic SC neurons in response to various visual stimuli. Our findings indicate that both Sst+ and Npnt+ respond to both looming and moving disks. However, Sst+ neurons favor larger moving disks, whereas Npnt+ neurons prefer smaller ones. In summary, our integrated technology platform streamlined a workflow that links spatial transcriptomics to connectomics at retinotectal synapses. TransA-MERFISH enables broad applications for dissecting the cell-type-specific wiring logic of the mammalian central nervous system.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

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Program #/Poster #: PSTR361.06/BB5

Topic: E.06. Vision

Support: NIH RO1EY027411
NIH RO1EY034001
NIH RO1EY026978

Title: Encoding of binocular disparity by narrow-field neurons in the mouse superior colliculus

Authors: *X. SONG[1], J.-C. HSIANG[2], D. KERSCHENSTEINER[3];
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Abstract: To capture prey, animals must localize rapidly moving targets in three dimensions and strikewithin a narrow range of distances. Binocular disparity — the offset between the two eyes'images of an object — is a powerful cue for distance, but where and how the brain extractsdisparity to guide rapid orienBng behavior is incompletely understood. While stereoscopicdepth percepBon is generally aDributed to recurrent corBcal processing, its demands may betoo slow to support ballisBc acBons. The superior colliculus (SC) is a conserved sensorimotorhub required for prey capture in mice, and its narrow-field (NF) neurons have been implicated indriving predatory behavior. Whether and how NF neurons compute binocular disparity,however, remains unknown. A neuron tuned to crossed disparity must integrate inputs fromnon-corresponding locaBons in the two eyes, predicBng that its monocular recepBve fields (RFs)should be spaBally offset. Here, we test this predicBon by recording from NF neurons in the SCof awake mice and mapping their spaBal RFs under interleaved binocular, ipsilateral-only, andcontralateral-only viewing on a hemispherical dome. We find that NF neurons exhibitsystemaBcally offset monocular RFs: the contralateral RF anchors the binocular RF posiBon,while the ipsilateral RF is shiRed nasally in azimuth, generaBng tuning for crossed disparity. Eye-tracking and geometric controls confirm that these offsets reflect circuit architecture ratherthan eye movements or apparatus misalignment. ConverBng the offsets into preferred objectdistances reveals a populaBon tuned to near space, with a median distance of ~4 cm —matching the stereotyped bite-and-grab strike distance — and a tail extending to ~20 cm acrossthe broader pursuit range. Two independent measurements, comparing contralateral-versus-ipsilateral and binocular-versus-ipsilateral RFs, converge on this tuning. By integraBngmonocular inputs with systemaBc spaBal offsets, SC narrow-field neurons compute crossedbinocular disparity to define the depth dimension of a three-dimensional acBon volume for preycapture.

Disclosures: X. Song: None. **J. Hsiang:** None. **D. Kerschensteiner:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.07/BB6

Topic: E.06. Vision

Support: NIH Grant R01EY025267
Walt and Lilly Disney Award for Amblyopia Research from the Research to Prevent Blindness Foundation

Title: Effects of amblyopia on synaptic input onto binocularly innervated neurons in the mouse superior colliculus

Authors: *M. EZEIZA-ORTEGA[1,2], J. W. TRIPLETT[1,2,3,4];
[1]Ctr. for Neurosci. Res., Children's Natl. Hosp., Washington, DC; [2]Neurosci. and Cognitive Sci., Univ. of Maryland, College Park, MD; [3]Dept. of Pediatrics, [4]Dept. of Pharmacol. and Physiol., The George Washington Univ., Washington, DC

Abstract: In amblyopia, an imbalance of acuity between the eyes leads to altered binocular vision. Years of work have demonstrated the impact of amblyopia on the primary visual cortex, but persistent deficits in visuomotor control suggest subcortical areas may also be affected. Recent work suggests that the superior colliculus (SC) is negatively impacted in human amblyopes, and monocular deprivation (MD) studies in mice suggest that SC neurons exhibit ocular dominance plasticity (ODP). However, the mechanisms underlying this plasticity and the extent to which different SC neuron populations express it remains unclear. To interrogate these open areas, we assessed the impact of MD on the density and localization of synaptic inputs onto neurons in the SC directly innervated by both eyes (SC-B). To model MD, we performed eyelid suture on mice during the critical period for ODP in SC. We labeled binocularly innervated SC neurons via an intersectional, trans-synaptic tracing strategy. To label excitatory and inhibitory pre- and postsynaptic proteins, along with axonal tracks from each eye, we utilized immunohistochemistry, bulk retinal labeling, and 7-color confocal microscopy. We quantified the changes in retinal axonal track volume and synaptic protein colocalization onto SC-B neurons following eyelid suture. Ongoing experiments indicate a decrease in deprived eye retinal axon volume in both the SC hemispheres of MD mice compared to the fellow eye or sham controls. Consistent with this, we found fewer excitatory synaptic contacts from deprived eye retinal inputs onto SC-B neurons in both hemispheres compared to sham conditions. Interestingly, we also found fewer fellow eye retinal synaptic contacts in the SC contralateral to the fellow eye, but no changes in the SC ipsilateral to the fellow eye nor in sham conditions. These data suggest that MD leads to hemisphere-dependent synaptic rewiring in the SC. Current work is focused in determining the changes in synaptic activity in binocular neurons in both hemispheres, along with quantification of non-retinal inhibitory and excitatory synapses onto binocular SC neurons in MD conditions.

Disclosures: M. Ezeiza-Ortega: None. **J.W. Triplett:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

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Program #/Poster #: PSTR361.08/BB7

Topic: E.06. Vision

Support: NIH Grant R01EY025627

Title: Determining the visually driven behaviors mediated by binocularly innervated neurons in the superior colliculus

Authors: *T. N. KEOPRASERT[1], M. EZEIZA-ORTEGA[2], J. W. TRIPLETT[2];
[1]Integrated Biomed. Sci., George Washington Univ., Washington, DC; [2]Ctr. for Neurosci. Res., Children's Natl. Hosp., Washington, DC

Abstract: Binocular vision is required for the execution of innate, ethologically relevant behaviors in mice, including visual threat avoidance and prey capture, both of which are regulated by the superior colliculus (SC). Previously, we found a surprising prevalence and diversity of binocularly modulated responses in the mouse SC. However, the neuronal wiring underlying these modes and how different subtypes of binocularly modulated SC neurons contribute to behavioral functions remain poorly understood. To begin to fill in these gaps, we developed a trans-synaptic, intersectional tracing paradigm to access SC neurons receiving direct input from both eyes. We injected AAV1-Cre or AAV1-FlpO into different eyes and Cre- and FlpO-dependent viruses encoding the inhibitory DREADD hM4Di or EGFP bilaterally in the SC. Mice were subsequently assessed in SC-dependent behavioral paradigms such as prey capture and the looming stimulus assay. Chemogenetic silencing of binocularly innervated SC neurons via administration of clozapine-N-oxide (CNO, 1 mg/kg) produced limited effects on visually guided behaviors. In the prey capture assay, we did not observe differences in overall capture latency, distance traveled, or approach distance compared to the saline-treated condition. Similarly, defensive responses to looming stimuli were largely unaffected by neuronal silencing. No significant differences were observed in escape latency, hiding time, or freezing behavior across looming stimulus speeds in trials conducted after CNO treatment compared to those performed after saline administration. Together, these findings suggest that binocularly innervated SC neurons are not required for the execution of prey capture or looming-evoked defensive behaviors. These results provide insight into the circuit basis of innate behaviors and suggest that binocularly modulated SC neurons wired in distinct ways may drive these visually guided behaviors.

Disclosures: T.N. Keoprasert: None. **M. Ezeiza-Ortega:** None. **J.W. Triplett:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.09/BB8

Topic: E.06. Vision

Support: NIH-NINDS U01NS122040

Title: Tectopulvinar Parallel Circuits in the Tree Shrew

Authors: *R. ROBERTS, A. KIPCAK, D. ARUN PRAKASH, C. BYRDSONG, A. ERISIR; Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: The Superior Colliculus (SC) or tectum, integrates sensorimotor information from the cortex and retina, and projects to the pulvinar via wide-field neurons (WF). Pulvinar then routes

this information to various cortical and subcortical targets involved in avoidance and approach behaviors. Previous work in the pre-primate species, the tree shrew, indicates that the circuitries underlying these behaviors are anatomically distinct where the caudal pulvinar (Pc) receives topographic WF projections, while the dorsal pulvinar (Pd) receives additional non-topographic WF projections. However, whether these two projection types originate from two WF subtypes remains to be explored. In order to address this question, we first injected retrograde AAVs to the tectorecipient pulvinar (Pd+Pc) and identified two populations using clustering analysis based on the soma sizes: bigger cells (minority) and smaller cells (majority), both of which were spread across the complete lateromedial extent of the SC. Restricting the injection to Pd resulted in retrogradely-labeled WF neurons more concentrated in the medial SC (representing the upper visual field), and revealed a shift in the distribution of soma sizes, yielding a larger proportion of bigger cells, suggesting that Pd-projecting WF neurons are larger than the population mean. To anterogradely examine the potential differences in WF terminal morphology, we co-expressed Cre recombinase and a Cre-dependent cytosolic peroxidase selectively in WF neurons using a CBLN2-promoter driven WF-specific AAV we recently developed. This allowed us to visualize the ultrastructure of WF terminals in the pulvinar, where they made synapses onto dendritic profiles located in both the Pc and Pd with unique characteristics. This also confirmed the presence of diffuse (non-topographic) projections to the Pd and specific (topographic) projections to the Pc as previously proposed. Finally, we confirmed using anterograde tract-tracing that Pd sends efferent projections to the Amygdala (BLA) in addition to the Striatum (Put, Cd) and cortex (TC, Ppr). Similar to their presynaptic WF counterparts, these projections also utilized Type-II vesicular glutamate transporter (vGluT2), supporting continuity across the tectopulvinar circuit. Overall, our results indicate that the tectopulvinar circuitry is segregated at the cellular and ultrastructural level, and are in support of two parallel pathways originating from WF neurons.

Disclosures: R. Roberts: None. **A. Kipcak:** None. **D. Arun Prakash:** None. **C. Byrdsong:** None. **A. Erisir:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.10/BB9

Topic: E.06. Vision

Title: A molecular marker for tectorecipient neurons in the dorsal lateral geniculate nucleus of the mouse (Mus musculus) and tree shrew (Tupaia belangeri)

Authors: *N. M. OLIVER[1], E. L. SAVIER[2];
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Abstract: Information in the primate visual system is projected from the retina to the thalamus and relayed to the visual cortex along the magnocellular (M), parvocellular (P), and koniocellular (K) pathways. Homologous organization is found across mammalian species, such as X, Y, and W pathways in carnivores. The contribution to vision of the K-pathway and its homologues remains poorly understood, but features atypical response properties and input from the superior colliculus (SC) at specific locations within the dorsal lateral geniculate nucleus (dLGN) of the thalamus. Although there have been morphological characterizations of cells in these regions, molecular definitions remain elusive. While the mouse serves as neuroscience's primary model organism due to its abundant experimental tools, its evolutionary distance from primates limits direct comparisons. To address this, the tree shrew provides a valuable intermediary between rodents and primates. In mice, SC inputs are restricted to the dorsal-most "shell" of the dLGN, which lacks lamination, whereas in tree shrews, SC inputs are distributed in specific layers of the dLGN, homologous to the K-layers of primates. Here, we present a molecular marker candidate for tectogeniculate neurons in both the mouse and tree shrew dLGN. Identified via single-cell RNA sequencing, and validated through retrograde and transsynaptic anterograde viral tracing combined with immunohistochemistry and RNA fluorescent in situ hybridization, our findings indicate that tectogeniculate neurons express this candidate marker gene. These results provide a molecular definition for K-pathway homologues in mouse and tree shrew, enabling more precise study of the parallel processing of visual information.

Disclosures: N.M. Oliver: None. **E.L. Savier:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

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Topic: E.06. Vision

Support: National Institutes of Health ZIA EY000511
National Institutes of Health ZIA MH002497-36

Title: Distinct long-range inhibitory and excitatory projections from the mouse superior colliculus

Authors: *K. K. COVER[1], L. WANG[3], R. F. PALETZKI[4], C. R. GERFEN[5], R. J. KRAUZLIS[2];
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Abstract: The superior colliculus (SC) is extensively connected with cortical and subcortical nuclei to facilitate a range of cognitive and sensorimotor functions. SC projection neuron targets vary by originating layer and topographic location. Here, we identify an additional dimension in in efferent connectivity: released neurotransmitter. We show that long-range GABAergic and

glutamatergic SC projection neurons produce distinct connectivity patterns in the mouse diencephalon, midbrain, and hindbrain. Inhibitory vGAT+ neurons strongly innervated lateral dorsal, reuniens, anterior pretectal, and red nuclei, as well as the inferior colliculus. Targets of weaker vGAT+ innervation included the lateral habenula, ventral anterior-lateral complex, and reticular nucleus. In contrast, excitatory vGlut2+ projections strongly innervated the ventral medial, parafascicular, and tegmental reticular nucleus, whereas weaker innervation was present in the central medial intralaminar nucleus as well as in several contralateral thalamic and hindbrain nuclei. In shared efferent targets, vGAT+ and vGlut2+ projections often innervated different subregions or differed in cross-hemispheric connections, notably in the zona incerta, lateral posterior, pedunculopontine, pontine reticular, periaqueductal gray, and tegmental reticular nuclei. These results collectively demonstrate an additional determinant of complexity in SC efferent connectivity in mice. Inhibitory projections may facilitate SC-mediated functions through mechanisms independently of, or in concert with, excitatory projections. Future work examining the functional roles of SC long-range inhibition stands to elucidate these mechanisms and their contributions to behavior.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.12/BB11

Topic: E.06. Vision

Support: ZIA EY000511

Title: A viral approach for optogenetic manipulation of retinal afferents in the primate visual system

Authors: *L. N. KATZ[1], R. J. KRAUZLIS[2], S. L. BOYE[3], S. BOYE[4];
[1]NIH, Bethesda, MD; [2]Natl. Eye Inst., Bethesda, MD; [3]Powell Gene Therapy Center, Dept. of Pediatrics, [4]Univ. of Florida, Gainesville, FL

Abstract: Intravitreal delivery of adeno-associated virus (AAV) offers a way to access retinal ganglion cells (RGCs) for studies of visual circuits and to develop retinal therapies. Previous work has identified AAV capsids and promoters that drive expression in primate RGCs after intravitreal injection. A remaining question is whether this route of administration can be used to express an optogenetic actuator in RGCs and their axon terminals in central visual targets. Here, we tested whether an AAV encoding the light-sensitive, inhibitory opsin Jaws could drive expression in the retina and in retinorecipient targets.
A rhesus macaque received an intravitreal injection of AAV.DGEDF-hSyn1-Jaws-KGC-ER2-tdTomato-WPRE, an engineered AAV capsid containing a construct optimized for axonal

transport. Expression was monitored *in vivo* with fundus imaging. tdTomato signal was detectable 2 weeks after injection and remained visible until tissue collection at 3 months, without obvious decay. The signal formed a ring-like pattern around the foveal pit at approximately 1-2° eccentricity, consistent with previous reports of intravitreal AAV transduction. Retinal flat-mount histology showed labeling consistent with the fundus images, along with additional labeling at more peripheral locations.
Histological analysis of the brain revealed labeled RGC terminals in multiple retinorecipient structures. In the lateral geniculate nucleus (LGN), Jaws/tdTomato expression was observed in magnocellular and parvocellular laminae corresponding to the injected eye. In the superior colliculus (SC), expression formed a dense superficial band just below the tectal surface, spanning the stratum zonale and stratum griseum superficiale. A fainter tier of labeling was present approximately 300-500 μm deeper, in the stratum opticum. Labeling was also observed in other retinal targets, including the nucleus of the optic tract.
These results show that intravitreal AAV delivery can express a light-sensitive inhibitory opsin in primate RGCs and their axon terminals in the LGN, SC, and other retinal targets. This approach provides a practical method for optogenetic manipulation of retinal inputs to subcortical visual circuits. It also has relevance for the development of retinal therapies to treat ocular disorders of visual function.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

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Title: Single neuron features revealed in multiunit macaque LGN recordings by cone-resolved mapping

Authors: *K. M. RAMSEY[1], L. C. SINCICH[2];
[1]Optometry and Vision Sci., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Optometry and Vision Sci., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Using adaptive optics microstimulation techniques, we recently found parvocellular neurons in the macaque lateral geniculate nucleus (LGN) often have receptive field centers comprised of a single cone photoreceptor within 4° of the fovea (Ramsey et al. 2026). Unexpectedly, our cone-resolved mapping occasionally revealed multiple spatially separated cones that drove LGN neurons, suggestive of multiunit activity arising from single extracellularly recorded waveforms. Here, we explored the spatiochromatic attributes and physiological features of these recordings to understand if traditional "single unit" isolation may mask activity from multiple neurons. Extracellular recordings were made from parvocellular LGN layers in 3 male macaques responding to binarized white noise movies delivered 0.34°-4.26° from the fovea using an adaptive optics scanning laser ophthalmoscope (AOSLO). Offline spike sorting isolated 55 waveforms and spike triggered average (STA) maps were computed from each. Eleven waveforms yielded STAs with 2-4 isolated responsive regions localized to single cones (2.25 ± 0.68 regions per map). The scatter of these regions across the cone mosaic averaged 24.2 ± 10.2 μm within any given STA map (equivalent to 3-4 cones apart) and did not scale with eccentricity. Six STA maps contained a mixture of ON and OFF responsive regions, which is inconsistent with parvocellular neurons being exclusively of ON or OFF type. Seven maps had regions responding to different wavelength components (red vs. green). Together, these results indicate these 11 waveforms were multiunit recordings, with each responsive region corresponding to the receptive field of a parvocellular neuron whose activity could not be distinguished by the spike waveform alone. Under this interpretation, these recordings contained 24 unique LGN neurons (10 ON, 14 OFF), 6 of which responded exclusively to red stimuli (710 ± 12 nm), 4 to green (543 ± 11 nm), and 14 to both. Average waveforms had peak-to-trough signal-to-noise ratios of 3.82 ± 1.39, which is commonly high enough to identify single unit recordings. Absent adaptive-optics correction, blurring of stimuli from natural optics could easily drive simultaneous activity from these closely spaced, near-foveal receptive fields. In addition, multiunit STAs with scattered receptive fields are a potential mechanism by which orientation sensitivity in LGN neurons may be observed. Thus, our results suggest that spike sorting and waveform shape alone may not guarantee the isolation of single neurons when recording in the early visual system.

Disclosures: K.M. Ramsey: None. **L.C. Sincich:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

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Program #/Poster #: PSTR361.14/BB13

Topic: E.06. Vision

Support: NIH NEI R01-EY036825
AFOSR FA9550-21-1-0230

Title: Neural response static nonlinearities in macaque RGCs and LGN neurons recorded in vivo

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[1]Optometry and Vision Sci., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Optometry and Vision Sci., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: In many models of how neurons respond to their input, a key feature is the function that relates the instantaneous inputs to a cell's firing rate, often called the static nonlinearity. Studies in retinal ganglion cells (RGCs) have extensively characterized static nonlinearities for different cell types, with nearly all of this work being conducted *in vitro*. We analyzed data recorded *in vivo* from macaque RGCs and neurons in the lateral geniculate nucleus (LGN) to quantify their static nonlinearities in response to naturalistic visual stimuli and to learn how these nonlinearities are transformed across the retinogeniculate synapse. Using responses to one-dimensional, receptive field center restricted 1/*f* luminance noise, we computed temporal spike triggered averages (STAs) of 8 RGC axons in the optic tract (3 OFF, 5 ON), and 9 connected RGC-LGN pairs from retinally driven EPSPs and LGN spikes (3 OFF, 6 ON). Stimulus luminance contrast spanned 2.4 log units, and each cell's preferred color was used during recordings (Sincich et al. 2007). To account for bias in the STA caused by stimulus correlations, we estimated the stimulus autocovariance structure and applied ridge-regularized inversion to obtain a decorrelated STA (dSTA). We then projected the original stimulus through each dSTA to obtain a generator signal, and revealed the static nonlinearity by plotting a neuron's firing rate as a function of its generator value. These nonlinearities all had a sigmoidal shape indicating saturation at high generator values, so we fit them with a logistic function and a Gompertz function to assess if the nonlinearities were symmetric around the mean generator signal. The Gompertz fits best captured the asymmetric decelerating response growth of the static nonlinearities and exhibited systematic response differences in the paired RGC-LGN cells. Analysis across pairs showed that the LGN nonlinearity was well explained by three simple transformations of the RGC nonlinearity: a firing rate decrease of -2.49 ± 5.25 Hz, a gain change factor of 0.64 ± 0.21, and lowered sensitivity of 0.15 ± 0.14 generator signal units. In summary, our results provide the first characterization of static nonlinearities in macaque RGC and LGN neurons *in vivo* as well as the nature of the transformations from an RGC and its companion LGN cell. LGN static nonlinearities appear to be transformations of RGC nonlinearities that involve lower firing rates, gains, and sensitivity to visual stimuli. The consistently asymmetric sigmoidal shape of the nonlinearities indicates that decelerating responses are typical, which differs from recordings made *in vitro* where static nonlinearities are usually accelerating.

Disclosures: E.W. Addai: None. **L.C. Sincich:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

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Topic: E.06. Vision

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NIH R01EY036242
NIH P30 EY012576

Title: Behavioral State Co-Modulates Thalamic Bursting and LGN-V1 Beta Oscillations in Macaque Monkeys

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[1]Univ. of California, Davis, CA; [2]Univ. of California, Davis, Davis, CA; [3]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA

Abstract: The lateral geniculate nucleus (LGN) is the main conduit by which signals from the retina are conveyed to primary visual cortex (V1). Through the convergence of cortical and subcortical extraretinal modulatory influences, the LGN functions as a dynamic gate that regulates the transmission of retinal information according to behavioral demands. In general, sensory transmission through the LGN is diminished during periods of reduced network engagement. Two prominent features of the LGN-V1 network are thalamic bursts and coherent LGN-V1 beta oscillations, both of which are also modulated by behavioral state. While it is generally accepted that thalamic bursts are most frequent during non-REM sleep, we have recently shown that LGN burst frequency in macaque monkeys is modulated across changes in behavioral demands during wakefulness. Likewise, we have recently demonstrated that LGN-V1 beta oscillations are modulated by similar changes in behavioral state. Specifically, beta oscillations are strongest when the network demands are low (i.e., decreased behavioral arousal, attention directed toward a different retinotopic location) and weakest when network demands are high. Based on these data, we proposed that LGN-V1 beta oscillations represent a signature of suppression that occurs when network engagement is low or during active distractor suppression. This hypothesis makes a strong prediction about the relationship between thalamic bursts within the LGN and LGN-V1 beta oscillations. Specifically, because LGN bursts require the hyperpolarization-dependent de-inactivation of T-type Ca^{2+} channels, and because beta oscillations are hypothesized to reflect a suppressed network state, thalamic burst frequency should increase with beta oscillatory power. To test this prediction, we analyzed extracellular LGN recordings from six rhesus monkeys, collected under a variety of behavioral conditions. Consistent with previous findings, both beta oscillatory power and thalamic burst frequency increased as behavioral demands decreased. This shared modulation produced a positive correlation between beta-band power and burst frequency across conditions. Ongoing analyses are aimed at determining whether this relationship extends beyond their common dependence on behavioral state and reflects a direct mechanistic link between beta oscillations and thalamic bursting within the LGN-V1 network.

Disclosures: H.J. Alitto: None. **M.M. Stroud:** None. **W. Usrey:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

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Topic: E.06. Vision

Support: NIH Grant: R01EY009593
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Title: Visuotopic organization of the murine dorsal lateral geniculate nucleus

Authors: *R. DAKWALA[1], Y. MIAO[2], A. GORIN[3], F. T. SOMMER[4], J. A. HIRSCH[5]; [2]Neurobio., [1]USC, Los Angeles, CA; [3]USC, Los Angeles, CA, ; [4]Univ. California, Helen Wills Neurosci Inst., Helen Wills Neurosci. Institute, UC Berkeley, Los Angeles, CA; [5]Neurobio., Univ. of Southern California, Los Angeles, CA

Abstract: Highly visual mammals rely on binocular vision to thrive, with the sharpest acuity achieved at specialized retinal regions that represent the central visual field-such as the fovea in primate and the area centralis in cat. This organization is relayed from station to station in the early visual hierarchy, such that receptive-field sizes remain smallest centrally and scale with eccentricity [1-3] in the dorsal lateral geniculate nucleus (dLGN) and V1 [4, 5]. Mouse does not have a fovea or area centralis per se; however, the retinal region that represents frontal binocular space has a concentration of cells with relatively small receptive fields [6-8]. Moreover, recent studies emphasize the importance of binocular vision for essential behaviors such as pursuing and capturing prey [9-11].
In primate and carnivore, the vast majority of retinal ganglion cells have center-surround receptive fields and project to dLGN. By contrast, there is a vast array of ganglion cell types in mouse with varied receptive field structures, only a subset of these diverse cell types innervate dLGN [12]. Further, murine relay cells receive input from multiple classes of retinal afferents [13-15]. To explore how retinal specializations are integrated in murine dLGN, we asked how visual response properties varied over visuotopic space. Our approach involved recording with multiconductor silicon probes and using various visual stimuli (sparse and dense noise, chirp, etc.) along with custom computational tools to gauge receptive field size, type, and dynamics. First, we assigned responses to either binocular or monocular regions of visuotopic space. The most salient result was that average receptive field size in the binocular zone was significantly smaller than in monocular regions. Now we are exploring how spatial and temporal aspects of receptive fields vary across space and, more locally, are asking if different combinations of response types cluster together. This work will help explain the general framework for organizing visual information as a function of visutopic space across species.
1.Connolly, M and D Van Essen, JCN 1984; 2. Sanderson, KJ, Exp Br Res,1971; 3. Soto-Sánchez, C., Nat. Comms, 2017; 4. Tootell, R, et al., J Nsci, 1988; 5. Tusa, RJ,et al., JCN 1978; 6. Gupta, D, et al., Nat Neuro, 2023; 7. Bleckert, A, et al., Curr Biol, 2014; 8. Gallego-Ortega, A, et al., Front Neuroanat, 2022; 9. Curr Biol ,2016; 10. Neuron, 2021; 11. Curr Opin Neurobiol, 2024; 12. Kerschensteiner, D and W Guido, Vi. Neurosci ,2017; 13. Jiang, Q, et al., Curr Biol, 2022; 14. Rompani, SB, et al., Neuron, 2017; 15. Liang, L, et al., Cell, 2018.
YM initiated the project which is continued by RD. AG contributed results.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.17/BB16

Topic: E.06. Vision

Support: EY007125

Title: Elevated Ocular TNF-alpha Levels and Altered Visual Processing: Implications for Schizophrenia

Authors: *T. MCDONALD[1], F. BRIGGS[2];
[1]Neurosci., Univ. of Rochester, Rochester, NY; [2]Lab. of Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: Schizophrenia is a severe neuropsychiatric disorder that is characterized by multiple visual system changes. The causes of these changes are unknown, however elevated systemic levels of TNFα, an inflammatory cytokine, have been reported in drug-naïve, first-episode schizophrenia patients. When released by microglia in the retina, TNFα is known to promote the death of retinal ganglion cells which in turn has been linked to degenerative effects along the feedforward visual system pathway, some of which are consistent with altered visual response properties frequently observed in people with schizophrenia. In this study, we report on a new animal (ferret) model that tests the hypothesis that retinal neuroinflammation can generate many of the visual system changes observed in people with schizophrenia. Using optical coherence tomography, electroretinography, and single-neuron recordings, we are assessing the structural and functional alterations to early visual structures (retina, visual thalamus, primary visual cortex) following the elevation of TNFα levels in the eye after intravitreal injection. Preliminary results suggest that intravitreal injection of TNFα produces significant retinal hypertrophy and altered contrast sensitivity yet no significant changes in visual response properties (i.e., maximum firing rates, spontaneous firing rates, preferred spatial frequency, and preferred temporal frequency) of contralesional cells of the lateral geniculate nucleus. Taken together, these findings demonstrate that our ferret model successfully recapitulates several visual deficits characteristic of first-episode psychosis.

Disclosures: T. McDonald: None. **F. Briggs:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.18/BB17

Topic: E.06. Vision

Title: Interspecies comparison of cholinergic axon densities in the lateral geniculate nucleus of primates

Authors: *M. BRAMEL, C. C. SHERWOOD;
Anthrop., The George Washington Univ., Washington, DC

Abstract: Primate vision has been shaped by selective pressures in an ancestral arboreal, fine-branched niche, resulting in visual adaptations for forelimb grasping and reaching. Unlike many other mammals, primate vision also plays a central role in mediating social interactions through facial gestures and body postures, with high acuity required to maintain social bonds. The lateral geniculate nucleus (LGN) is the first-order thalamic relay for visual information, integrating retinal input and modulatory afferents before cortical processing in the primary visual cortex (V1). Cholinergic innervation regulates visual signal transmission and refines acuity, but the distribution of these axons remains poorly understood across primate species. This study compares the quantitative density of neurons and cholinergic afferents in the LGN of common marmosets, rhesus macaques, chimpanzees, and humans using stereological approaches. While overall species differences in neuron density were observed, the relationship between magnocellular and parvocellular layers stayed constant across species. Catarrhines clustered together in neuron density, with marmosets as a significant outlier (marmoset - macaque: $g = -8.950$; marmoset - chimpanzee: $g = 7.899$; marmoset - human: $g = 6.523$). Differences in cholinergic axon density across the species were not observed. Thus, cholinergic innervation per neuron ratios varied by species ($p = 0.002$), with marmosets exhibiting lower axon length density per neuron than catarrhines. This species-specific variation could be due to differing evolutionary pressures between catarrhine and platyrrhine lineages, or differences in cholinergic innervation scaling between small-brained and large-brained primates. A large-brained platyrrhine, the tufted capuchin, is currently being added to the study. Given the widespread use of nonhuman primates as models for the human brain, these findings highlight the importance of species-specific variation and caution against assuming uniformity in brain regions across primate species.

Disclosures: M. Bramel: None. **C.C. Sherwood:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.19/BB18

Topic: E.06. Vision

Support: Intramural Research Program of the National Institute of Mental Health ZIAMH002898

Title: Fetal rAAV delivery enables broad genetic access to the primate retina

Authors: *A. RIBEIRO GOMES[1], J. PERRONE[1], S. MASTWAL[1], T. B. USDIN[2], D. A. LEOPOLD[1];
[1]Section on Cognitive Neurophysiol. and Imaging, Systems Neurodevelopment Lab., [2]Systems Neurosci. Imaging Resource, NIH, Bethesda, MD

Abstract: Vision is the primary sensory modality in humans and other primates, shaping important interactions with the physical and social environment. As such, primate eyes and brains have evolved specialized circuits and regions that diverge substantially from other mammals. As a result, the wealth of findings from mouse genetic studies on cell types and their contributions to vision has limited translational relevance to primates. Yet, studying the detailed wiring and function of primate visual circuits remains restricted by limited genetic access. In the primate retina, viral vector-based approaches lead to overall low transduction efficiency and spatially restricted gene delivery, limiting both basic research and clinical applications. Here we introduce an intravitreal fetal delivery approach that enables robust transgene expression in the primate retina. In our previous study (Ribeiro Gomes et al., 2026), we demonstrated that administration of recombinant adeno-associated virus (rAAV) vectors into the developing primate brain leads to broad gene delivery. Building on this approach, we used ultrasound guidance to deliver rAAV vectors prenatally to the retina of fetal marmosets, small New World primates whose visual system shares key developmental, anatomical, and functional features with that of humans. We found that a single injection of naturally occurring rAAV serotypes resulted in dense transduction across the retina. In particular, retinal ganglion cell (RGC) populations spanning both central and far-peripheral visual fields were efficiently labeled, allowing visualization of retinofugal projections entering the brain and projecting broadly across target sites in the hypothalamus, thalamus, and midbrain. We are presently applying this method to gauge retinofugal circuit refinement by comparing RGCs projections in twins transduced in the same procedure but evaluated either immediately after birth or after one year. These findings highlight the potential of prenatal rAAV delivery for widespread genetic access to the primate retina and its projections, opening new opportunities for longitudinal studies of visual circuit development, organization, function, and genetic manipulation across the lifespan.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

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Program #/Poster #: PSTR361.20/BB19

Topic: E.06. Vision

Support: NEI Intramural Research Program EY000311

Title: Olfactomedin 2 regulates axon maturation and retinofugal circuit architecture in mouse visual system

Authors: *J. NIE, K. LOFTIS, N. NAKAYA, S. I. TOMAREV;
Natl. Eye Inst., NIH, Bethesda, MD

Abstract: Olfactomedin 2 (Olfm2) is highly expressed in developing retinal ganglion cells (RGCs) and becomes downregulated in the eye after birth, suggesting a role in the maturation of retinal output pathways. Although Olfm2 has been implicated in ocular and neuropsychiatric disorders, its role in axon maturation and retinofugal circuit architecture remains unclear. Here, we characterized structural and anatomical phenotypes in *Olfm2* knockout (KO) mice using optical coherence tomography (OCT), electron microscopy, retinal whole-mount analysis, cholera toxin B (CTB)-based anterograde tracing, tissue clearing, and whole-brain light-sheet imaging, and compared them with wild-type (WT) mice. Despite normal RGC numbers at both postnatal week (PW) 7 and PW32, *Olfm2* KO mice at PW7 exhibited significantly reduced axon caliber and hypomyelination in both the optic nerve and optic radiation. G-ratio analysis demonstrated significantly increased g-ratios in large-caliber axons (>1.0 μm) in the optic nerve, whereas increased g-ratios were observed across all axon calibers in the optic radiation, consistent with thinner myelin sheaths (all $p < 0.05$). At PW17, OCT imaging revealed a thinner retinal nerve fiber layer (RNFL) in *Olfm2* KO mice than in WT mice ($p < 0.01$). Whole-brain light-sheet imaging following CTB tracing revealed significantly reduced CTB-labeled projection volume in the optic chiasm, dorsal and ventral lateral geniculate nuclei, olivary pretectal nucleus, and superior colliculus of PW7 KO mice compared with WT mice (all $p < 0.05$). These differences between KO and WT mice were less pronounced at PW32. The preservation of RGC numbers alongside abnormalities in RNFL thickness, axon myelination, and retinofugal projection volume suggests that Olfm2 regulates the establishment and maturation of retinal output pathways rather than neuronal survival. Together, these findings identify Olfm2 as a regulator of axon maturation and retinofugal circuit architecture and support a developmental role for Olfm2 in the establishment of visual pathway connectivity.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

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Title: Reciprocal pulvinar circuits link visual and visuomotor cortices in the macaque brain

Authors: *S. ZIEGLER[1], B. AHMED[2], T. YE[4], Z. SHEN[5], A. J. PARKER[3], K. KRUG[6]; [1]Otto-von-Guericke-University Magdeburg, Magdeburg, Germany; [3]Physiology, Anat. and Genet., [2]Univ. of Oxford, Oxford, United Kingdom; [4]ION, CEBSIT, CAS, Shanghai, China; [5]ION, CEBSIT, CAS, Shanghai City, China; [6]Sensory Physiol., Otto-von-Guericke-University, Magdeburg, Germany

Abstract: The pulvinar is a large subcortical structure in the primate brain with extensive cortical connectivity. Although its precise function remains debated, the pulvinar is thought to contribute to sensorimotor integration. Of particular relevance, the pulvinar is strongly interconnected with visual and visuomotor cortices central to perceptual decision-making, including extrastriate visual area V5/MT and the lateral intraparietal area (LIP). The dorsal and ventral subdivisions of LIP (LIPd and LIPv) are structurally and functionally distinct; LIPd receives input predominantly from ventral stream visual areas, while LIPv is more strongly connected to dorsal stream visual areas, including area V5/MT. In addition to direct cortico-cortical projections, communication between these regions may be mediated through pulvinar pathways. To determine whether LIP and V5/MT receive input from similar pulvinar regions, small volumes of Cholera Toxin B (CTB; low salt, List Biological Laboratories; n = 7) or Fast Blue (n=1) were targeted to LIPd or LIPv, or to V5/MT, in anesthetized macaques. Following transcardial perfusion with 4% paraformaldehyde, parasagittal or coronal brain sections were immunohistochemically processed, and the pulvinar was examined for retrogradely-labeled neuronal cell bodies. CTB injections into LIPd resulted in widespread labeling in dorsal pulvinar across a wide medio-lateral extent, whereas injections into LIPv produced sparser, more spatially clustered labeling in the same region. Little to no label was observed in the inferior pulvinar. In contrast, injections into V5/MT yielded robust labeling in the inferior pulvinar, highlighting the specificity of these pathways for early to mid-level visual processing. However, projections reconstructed across animals also suggested partial overlap of retrogradely labeled neurons within the lateral pulvinar, indicating that this region projects to V5/MT as well as to both LIP subdivisions. Retrograde tracing data from two macaques using fluorescent-labeled CTB injections into pulvinar confirmed reciprocal connectivity with V5/MT and LIP. Specifically, injection into medial pulvinar revealed dense connectivity to LIPd, less with LIPv, and none with V5/MT, while injection into inferior pulvinar revealed moderate connectivity to LIPv and V5/MT. These data further suggest that cortico-pulvinar inputs appear to be organized more specifically with respect to pulvinar subdivisions than the reciprocal pulvino-cortical outputs, which are distributed more broadly. Together, these findings provide evidence for an anatomical connection between LIP and V5/MT routed via the pulvinar.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

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NIMH 2R01MH064043
NIMH P50MH109429

Title: Pulvino-cortical dynamics during shape processing

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Abstract: Pulvinar establishes extensive reciprocal connections along the ventral visual stream, yet the functional roles of these circuits are unclear. Contrasting ideas have supported a variety of roles for pulvinar, suggesting that it may gate sensory input, facilitate cortical maintenance, or strictly relay feedforward signals. However, how these putative functions may integrate into moment-to-moment processing of sensory input remains elusive. Furthermore, while pulvinar has been shown to exhibit fast selective responses to some object categories, the magnitude of these responses, relative to cortex, and how they integrate with cortical processing at the population level has not been probed. Here, we investigated these interactions by performing simultaneous electrophysiological recordings in receptive-field matched sites within the pulvinar and the dorsal posterior inferotemporal cortex (PITd) of two macaques viewing multi-category shape stimuli. Using decoding analyses, we found that pulvinar neurons exhibit robust shape selectivity that equals, and occasionally surpasses, that of their cortical counterparts. Latency analyses of the decoding time-courses revealed that pulvinar encoding consistently lagged behind PITd in the initial response following stimulus onset. Critically, communication subspace analyses identified a pulvino-cortical subspace that, upon virtual lesioning, significantly reduced shape-encoding in PITd. Further, cross-temporal decoding analyses showed that pulvinar led PITd following the evoked period where pulvinar activity was predictive of future PITd activity, but not vice-versa. These results suggest that pulvinar provides a delayed modulatory signal, serving to sustain cortical information representations following the initial stimulus-evoked transient.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

Location: WCC Halls A-C

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Program #/Poster #: PSTR361.23/BB22

Topic: E.06. Vision

Support: P50MH132642
RO1 EY017699
R01 MH137624

Title: Widespread cortical high-frequency activity during spatial attention is aligned to pulvinar theta phase in human iEEG

Authors: *F. BARTSCH[1,2], J. GAO[1], R. BOSHRA[2], K. BANAIE BOROUJENI[2], N. BRYSON[3], L. YING[2], X. LIU[2], N. BENTLEY[5], J. T. WILLIE[4], P. BRUNNER[6], R. T. KNIGHT[7], S. KASTNER[2];
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Abstract: Modulation of high-frequency activity (HFA) underlies many cognitive processes, in particular selective attention. Attention in general provides salient signals to investigate the larger question of how different cortical and subcortical brain regions interact during cognitive processes. A particular feature of interest is that HFA, even when observed across large cortical regions, tends to be phase-locked to low-frequency rhythms, particularly in the theta (4-8 Hz) range. However, the mechanisms underlying this synchronization of HFA across distributed brain regions remain unclear, especially in the cases of cortical areas that only have weak direct connections. We hypothesize that higher-order thalamic nuclei—especially the pulvinar—play a key role in coordinating this long-range synchronization by entraining outgoing signals to separate cortical regions through theta-band oscillations.
Here, we approach this question in intracranial recordings in humans. We analyzed cortical and thalamic responses from intracranial electrodes implanted in 12 epilepsy patients while they performed a visual spatial attention task (i.e. Egly-Driver task) where visual cues signaled the likely location of upcoming targets. We preprocessed this data using data-driven, clustering-based referencing, which identifies both unique and structurally shared signals in iEEG recordings. We then used a previously described algorithm to identify short-duration, high-amplitude bursts of HFA (which are comparable but use a more general definition than ripples described in the literature).
We observe that both cue and target presentation reliably elicits theta oscillations in the pulvinar and HFA bursts across multiple cortical regions. Furthermore, we find that cortical bursts are significantly phase-locked to the rising phase of pulvinar theta, and that pulvinar theta is stronger when bursts co-occur in multiple regions. We interpret this result as a processing cascade where pulvinar theta is used to synchronize cortical bursts, which in turn reinforce the theta oscillation in thalamus. Additionally, we see that theta phase extracted from different pulvinar subnuclei is locked to bursts in different cortical subnetworks, reflecting underlying thalamocortical connectivity. Finally, we present preliminary results that there is homogeneity among the properties of bursts that may vary depending on the brain region and networks they are a part of. These findings provide novel insight into the role of the thalamus in coordinating cortical activity during attention by leveraging low-frequency oscillations to facilitate inter-areal communication.

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Poster

PSTR361: Visual Pathways: Subcortical and Others

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Topic: E.06. Vision

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Title: Neural circuits for robust visual object detection

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Abstract: The brain can detect and recognize objects across a large range of visual and behavioral contexts, even as low level properties of the object like position, lighting, and orientation change. Such robust object detection has been observed in individual neurons and incorporated into computational models for object classification. However, the biological mechanisms that allow neurons to detect objects across variable contexts are not well understood. Here, we study the cellular and synaptic mechanisms of robust object detection using the visual system of the fruit fly, *Drosophila melanogaster*. In the fly visual system, we can fully characterize the connectivity of visual circuits and target virtually any cell type for physiological characterization or perturbation. Using *in vivo* two photon imaging, we find that several classes of visual projection neurons show a selectivity for small moving objects that is invariant to displacements within the receptive field. We use the connectome to identify the major upstream inputs to these visual projection neurons and map them across visual space. We then use targeted recordings from these cells to characterize their feature selectivity and receptive field structure. Using measured connectivity and physiology, we construct biologically-constrained, linear-nonlinear cascade receptive field models to account for observed feature selectivity and invariances. We identify two important circuit features for shaping feature selectivity and translation invariance: first, nonlinear summation across spatial subunits that correspond to columnar excitatory inputs, and second, widefield feedforward inhibition that corresponds to local inhibitory interneurons. This work provides a highly biologically constrained computational model of translation invariance and allows us to connect distinct circuit elements to the computations that are critical for robust feature selectivity.

Disclosures: C. Porwal: None. **G. Valdivieso:** None. **M.H. Turner:** None.

Poster

PSTR361: Visual Pathways: Subcortical and Others

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Title: Neural activity constraints improve connectome- and task-constrained models of the fruit fly optic lobe

Authors: *L. ULMER[1], Z. STEFANIDI[1], I. OMOLAYO[1], B. KIM[1], M. MCGILL[2], B. NGUYEN[1], N. C. KLAPOETKE[2], A. NERN[2], J. LAPPALAINEN[1], S. TURAGA[2], J. H. MACKE[3,1];
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Abstract: Understanding how neural circuits in the brain give rise to computation requires models that integrate both structural and functional data. Connectome measurements of the fruit fly's visual system made it possible to build mechanistic network models with synaptic connectivity taken directly from the connectome, and free parameters optimized to perform a motion detection task [1]. Ensembles of such models can predict single-cell tuning properties, but individual models trained under same connectome and task constraints can converge to different functional solutions. Therefore, additional constraints, such as neuronal activity recordings, are needed to identify single-neuron function, especially when scaling to larger circuits.
Here, we present an approach for co-training connectome-constrained models of the fruit fly optic lobe [2] on both computational tasks and neural recordings. We used activity measurements from 50+ cell types across five studies, including calcium imaging [3,4], voltage recordings [5,6], and spatiotemporal receptive field measurements [7]. To combine these diverse data modalities with training on a motion detection task, we use recording-specific decoders tailored to each measurement type.
The resulting models accurately fit the neural recordings they are trained on, reproducing cell-type-specific activity across the circuit while maintaining task performance. Incorporating activity constraints also improves predictions beyond the training stimuli—for example, looming responses of visual projection neurons that were constrained only under different stimulus conditions during training are better captured than in models trained on task constraints alone. Together, these results demonstrate a framework for integrating diverse neural recordings into large-scale connectome-constrained models, enabling them to capture known functional properties across the circuit and generate hypotheses about the roles of cell types not yet experimentally characterized.

[1] Lappalainen et al. (2024) [2] Nern et al. (2025) [3] Klapoetke et al. (2022) [4] Ketkar et al. (2022) [5] Groschner et al. (2022) [6] Behnia et al. (2014) [7] Currier and Clandinin (2025)

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Poster

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Title: Recurrence and feature selectivity in the Drosophila visual system

Authors: *T. LUPASHINA, C. MICKELS, M. TURNER;
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Abstract: In nature, animals are capable of performing a great variety of intricate behaviors due in part to the ability of the nervous system to process sensory information across diverse behavioral and sensory contexts. In the visual system, such flexibility relies in part on neural feedback mechanisms, where brain signals from other regions modulate activity within the visual system according to visual conditions or behavioral goals. However, there is still a significant gap in understanding the biological mechanisms that contribute to and drive feedback in the visual system. Thanks to the extensive genetic and connectomic resources available in Drosophila, identified cells and circuits mediating visual feedback can be studied at the cellular and synaptic level. In flies, visual projection neurons (VPNs) act as local “feature detectors”, passing on information from the optic lobe to the central brain to drive visually guided behaviors. Visual system feedback is mediated by visual centrifugal neurons (VCNs), which originate in the central brain and relay signals back to the optic lobe. A subset of inhibitory VCNs form recurrent loops with synaptically connected VPNs, a circuit motif that we hypothesize modulates the feature-detecting properties of VPNs. Using the whole brain connectome, we identify recurrent feedback loops to the visual system, and then use in vivo two photon imaging of genetically targeted VCNs to confirm that these cells are visually responsive. Using predictive models constrained by measured synaptic connectivity, we show that the tuning of recurrent VCNs reflect the summed activity of their major VPN inputs. With predictive modeling and genetically targeted neuronal silencing experiments, we are further testing the hypothesis that recurrent inputs to VPNs shape visual feature tuning.

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Poster

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Title: Distinct roles of excitation and inhibition in spatial-frequency tuning dynamics in mouse visual cortex

Authors: *H. TANAKA[1], M. ABE[3], R. YASUI[2];
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Abstract: A major component of feature tuning in neurons of the primary visual cortex is established within a brief period following stimulus onset. Previous studies have suggested that intracortical inhibition plays an important role in this process. Specifically, tuning has been proposed to emerge through inhibitory inputs that lag behind excitation, giving rise to temporal changes in both preferred feature values and tuning bandwidth. However, it remains unclear how excitatory and inhibitory inputs interact over time during this critical period and how such interactions shape feature tuning. To address this issue, we investigated the role of intracortical inhibition in the formation of spatial frequency (SF) tuning in neurons of the primary visual cortex (V1), which exhibits one of the most prominent examples of temporal tuning dynamics. Using transgenic mice expressing halorhodopsin selectively in inhibitory neurons (Gad67-Cre/eNpHR3.0 mice), we optogenetically manipulated intracortical inhibition while recording spiking activities with multi-sites electrodes. Responses were measured for 300~400 ms following the presentation of a 50 or 100 ms flashed sinusoidal grating stimulus, encompassing both the transient response period and the subsequent response phase. We then analyzed in detail how the temporal evolution of SF tuning curves was affected by the removal of intracortical inhibition. Unlike previous hypotheses, we found that intracortical inhibition does not contribute to the generation of the temporal shift in optimal SF itself (population mean, control : 0.027~0.048 cpd, photo-condition 0.027~0.052 cpd, n=132 cells) during transient response period (80~200 ms after stimulus onset), indicating that these tuning dynamics were primarily determined by excitatory inputs. On the other hand, intracortical inhibition sharpened tuning curves throughout the response period. Furthermore, cortical inhibition effectively terminated neuronal responses at the point when the continuous evolution of the tuning curve had been completed by suppressing excitatory inputs tuned to lower spatial frequencies that emerged after the transient response (200 ms~). These findings identify the roles of excitation and inhibition on the temporal dynamics of SF tuning. They further demonstrate that intracortical inhibition not only enhance tuning selectivity but also plays a critical role in regulating the temporal structure of feature representations, thereby enabling feature transmission with high temporal precision and orderly progression.

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Poster

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Program #/Poster #: PSTR362.02/BB27

Topic: E.06. Vision

Title: Coordination of modular spontaneous activity across brain regions in the developing cortex

Authors: *C. J. APGAR, G. B. SMITH;
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Abstract: During early development, cortical networks exhibit organized spontaneous activity patterns thought to guide the formation of mature functional architecture. In the ferret visual cortex (V1), spontaneous activity prior to eye opening is modular and exhibits millimeter-scale correlations that predict later visually evoked functional organization. Similar spontaneous activity has been observed throughout developing sensory and association cortices, suggesting that distributed cortical regions may share common organizing principles. However, it remains unclear whether these activity patterns arise independently within local cortical circuits or reflect coordinated interactions across regions. To address this, we performed simultaneous widefield calcium imaging of GCaMP6s activity in ferret V1 and in either auditory cortex (A1) or prefrontal cortex (PFC) prior to eye and ear opening. We found that the temporal pattern of spontaneous activity between V1 and A1 was only weakly related, with simultaneous events occurring at chance levels. The spatial structure of overlapping events did not differ from events in which only one brain area was active, and both event types occupied similar low-dimensional subspaces, with cross-projection analyses revealing substantial shared variance between event classes. Strikingly, however, during events with co-incident activity, we found significant correlations in the spatial patterns of activity across regions, suggesting large-scale functional interactions that link specific activity patterns across brain areas. We observed similar results between V1 and PFC, with co-incident activity occurring at chance levels and showing similar low-dimensional activity patterns irrespective of the other region's activity state. Notably, as with A1, overlapping events in V1 and PFC exhibited cross-region spatial correlations, indicating large-scale network interactions across highly varied brain regions during early development. Together, these results suggest that spontaneous activity in the immature cortex is generated independently within local circuits, with specific patterns of activity influenced by large-scale cross-area interactions. These early cross-modal interactions may provide an organizing substrate for the later developmental emergence of distributed multisensory and cognitive functional networks.

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Poster

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Topic: E.06. Vision

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Title: Differential input bias from cortical regions into adult mouse primary visual cortex visual cortex based on retinotopy

Authors: *K. T. KONDA[1], H. LEE[2], H.-K. LEE[2];
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Abstract: Communication across the cerebral cortex is crucial to perceiving and providing context to the world. This is especially true for the Primary Visual Cortex (V1), but despite its well-defined retinotopy, little is known about the spatial bias in distribution of its many cortico-cortical connections. We used a combination of targeted viral injections, 3D whole-brain imaging, and automated cell detection to measure the input bias of 32 cortical and subplate regions of interest (ROIs) into the Anterior (A, n=8), Posterior (P, n=8), Medial (M, n=10), and Lateral (L, n=10) quadrants of the adult mouse V1. Taking advantage of the Ai14 mouse line's Cre-inducible tdTomato system, we targeted injections of retrograde viral vectors expressing Cre recombinase to one of the four cardinal locations of V1. At P90 to P120, fixed brains were cleared using the EZClear protocol, imaged using light-sheet fluorescence microscopy, and registered to the Allen Brain Atlas framework. Labeled cells were automatically detected and assigned to ROIs using BrainGlobe 3D image analysis software. Cell distributions along either the A-P or L-M axis were analyzed separately via permutation testing (10,000 shuffles). We found that 12 out of 32 ROIs had a significant differential input bias ($p < 0.05$), with the majority (9 of 12) polarized along the A-P axis. Among the other sensory cortices, the Primary Auditory Cortex was particularly interesting, as its inputs were significantly biased ($p = 0.0023$) to the medial region of V1, which corresponds to the established monocular zone. No regions were significant along both axes, although many areas trended toward one direction without reaching significance. Additionally, cell density mapping within the source regions revealed a distinct micro-topography mirroring their targeting within V1. We hope this work can provide an anatomical guide to optimize targeted electrophysiological recording and circuit manipulation. Altogether, our findings demonstrate that the retinotopic field provides a spatial scaffold to coordinate distinct cortical networks within V1.

Disclosures: K.T. Konda: None. **H. Lee:** None. **H. Lee:** None.

Poster

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Title: Layer-specific spatial coding in mouse primary visual cortex during virtual navigation

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Abstract: Although primary visual cortex (V1) is traditionally viewed as a sensory area encoding visual features, there are rich representations of local space encoded alongside retinal inputs. How spatial information is organized across V1 laminar architecture — and how this organization evolves with experience — remain poorly understood. Using two-photon calcium imaging in head-fixed mice navigating a virtual reality corridor, we simultaneously recorded neuronal activity across all cortical layers in V1. The virtual environment contained four visually identical landmarks leading to a reward at the end of the corridor, allowing us to dissociate spatial position from visual input. The majority of V1 neurons exhibited robust spatial modulation, responding differentially to identical visual stimuli dependent on their corridor position. Strikingly, deep layers (L5 and L6) showed stronger spatial modulation than superficial layers even in the earliest recording sessions. Superficial layers (L2/3 and L4) showed greater experience-dependent plasticity, gradually increasing spatial modulation across sessions. The earlier bias in deep V1 layers likely reflects top-down input from spatial areas such as retrosplenial cortex and hippocampal formation, which we are now exploring with targeted circuit manipulations. Beyond overall spatial modulation, landmark preferences in all layers shifted systematically across sessions, with population responses redistributing from early corridor landmarks toward the reward-proximal location. These results suggest that spatial coding in V1 reflects two complementary mechanisms: an innate, connectivity-driven bias in deep layers and experience-dependent plasticity in superficial layers, revealing an active role for V1 in navigation.

Disclosures: J. Yeo: None. **M. Goard:** None.

Poster

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Title: Local excitatory connectivity sets a 'column-like' spatial scale for recurrent amplification in V1

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Abstract: Recent work in the mouse primary visual cortex (V1) has identified strong excitatory-excitatory spatial connectivity over very short distances (the minicolumn scale; ~50 μm). However, the ways in which this narrow extent of excitation might influence representations on larger scales remains an open question. Here we combined two-photon imaging and holographic optogenetic perturbation with theoretical models to demonstrate that overlapping pairwise excitatory-excitatory (E-E) connectivity at the smaller minicolumn scale produces pattern amplification at a larger column-like scale (~300-500 μm). When we stimulated groups of increasing numbers of neurons, we found substantial amplification for stimulated patterns of this larger spatial scale (mean response in 10 cells shared across patterns: 10-cell pattern $\Delta F/F = 8.5 \pm 2.5\%$, 30-cell pattern $\Delta F/F = 21.6 \pm 3.1\%$, mean ± SEM, N = 4 animals). These amplification effects can be explained by sums of pairwise interactions at the 50-μm scale, as we demonstrate in recurrent network models with balanced excitation and inhibition. Our models predict that higher-density input patterns will produce stronger population responses, a finding which we confirmed experimentally. Finally, we saw evidence that larger responses during natural visual movies compared to gratings are related to this spatial clustering. During natural movie responses, strongly responding cells tended to have nearby co-active cells (cell counts within 30 μm, ratio of movie to full field grating = 2.78 ± 0.51, mean ± SEM, N = 3 animals). Maximal responses during natural movies were larger than maximal responses across a set of full field drifting gratings (same neurons, Δdeconv. spike rate = 6.8 ± 1.1, mean ± SEM, N = 3 animals).These results suggest that spatial clustering of cell responses during natural movies could be a mechanism for generating the strong responses seen in natural vision. Together, our experimental and theoretical work suggests a functional mechanism in cortical networks, where minicolumn-scale connectivity enables column-scale amplification, driving neurons to increased firing rates as nearby neurons are activated together.

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Poster

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Title: Whole arbor mapping of afferent-specific inhibitory synapses onto L2/3 pyramidal neurons in mouse visual cortex

Authors: *B. SCHMERL[1], Y. SHARAV[2], J. BOIVIN[4], M. LONDON[3], E. NEDIVI[4];
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Abstract: It is increasingly evident that inhibitory circuits play a key role in neurological function. However, the contribution of inhibitory synapses, and of inhibitory subtypes in particular, to dendritic to dendritic integration remains poorly understood. The majority of cortical Inhibitory signaling originates from GABAergic interneurons, characterized by selective expression of either Somatostatin (SST) or Parvalbumin (PV). While it is well established, that synaptic transmission differs functionally between these classes, studies examining their cellular targeting onto pyramidal neurons are often limited in resolution and/or coverage of the dendritic arbor.
Here we used Cre-dependent Synaptophysin-TdTomato expression to comprehensively label inhibitory subtype-specific presynaptic boutons synapsing onto sparsely labelled, YFP-cell filled pyramidal neurons in Layer 2/3 of binocular mouse visual cortex. Synaptic contacts were then validated and proteomically characterized with epitope-preserving Magnified Analysis of Proteome (eMAP), a combination of tissue clearing and expansion microscopy, allowing super-resolution analysis. We were thus able to map the sub-cellular distribution of inhibitory synapses across the whole dendritic arbor of pyramidal neurons in relation to their inhibitory afferent identity.
Contrary to the canonical view, we found that SST synapses account for only two thirds of dendritic inhibitory synapses, and that the remaining synapses largely come from PV-expressing interneurons. In addition to innervating the soma, PV accounts for 25% of the dendritic inhibition of pyramidal neurons. Further, we see that subtype-specific synapses are heterogeneously distributed across individual dendrites with subtype-specific differences in synaptic clustering.
These results are an important contribution to defining subtype-specific distribution of inhibitory synapses, and their distinct roles have important implications for the modeling of dendritic computation and circuit function.

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Poster

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RPB-Stein Award

Title: The Logic of Thalamic Inputs onto the Molecular Taxonomy of Cortical Neurons Reveals a Visual Hierarchy

Authors: ***X. GE**[1], X. WEI[2], B. RUAN[1], Q. WU[1], S. CHANG[3], N. TSAI[1], X. DUAN[1], M. SCANZIANI[4];
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Abstract: The hierarchical organization of sensory cortices and the rich molecular taxonomy of their cell types are defining features of the mammalian cortex. Cortical areas along this hierarchy are reciprocally connected via the thalamus through bottom-up and top-down projections. The logic through which these projections map onto the cellular taxonomy of the cortex is, however, poorly understood. Here, we combined an anterograde transsynaptic tracer with spatial transcriptomics in the mouse visual system to spatially register and molecularly classify downstream neurons from regionally defined starter neurons. We applied this approach to study thalamocortial circuits, where the dorsolateral geniculate nucleus (dLGN) provides the quintessential bottom-up thalamic input to the primary visual cortex (V1), whereas the pulvinar thalamic nucleus (LP) serves as a hub for bottom-up and top-down projections to visual areas along the hierarchy. We discovered that distinct thalamic inputs target characteristic sets of molecularly defined cortical neurons, forming bottom-up or top-down “signatures” defined by cell-type composition and the ratio of GABAergic to glutamatergic neurons. These signatures reveal a hierarchy spanning thalamic nuclei and visual cortical areas, independently predicted by the molecular and cellular similarities between cortical areas. This work uncovers basic principles of how bottom-up and top-down thalamic inputs map onto the cellular taxonomy in the visual cortex and establishes a cellular framework for the cortical hierarchy.

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Poster

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Title: Top-down modulation of visual cortical processing during visual backward masking in mice

Authors: *S. C. GNODDE, L. KROEZE, J. C. FRANCKEN, T. STEIN, U. OLCESE;
Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: A central question in consciousness research is how interactions between higher-order cortical areas and sensory cortex give rise to perceptual experience. Recurrent feedback from prefrontal cortex (PFC) to the primary visual cortex (V1) has been proposed to play an important role in conscious visual perception, yet this remains heavily debated. Here, we investigate how selective inhibition of neurons projecting from the anterior cingulate cortex (ACC, a prefrontal area implicated in perceptual decision-making and attention) to V1 affects neuronal activity and visual encoding in V1. We further examine whether the resulting changes in V1 response dynamics and stimulus encoding resemble those observed during visual backward masking. Head-fixed mice were trained on a visual localization task. In a subset of trials we included a visual backward masking protocol, in which a briefly presented target stimulus was followed by a mask after a few milliseconds. To causally manipulate top-down signaling, projection-specific optogenetic inhibition was used to silence feedback-projecting neurons from ACC to V1 for 200 ms during stimulus presentation. Simultaneously, Neuropixels recordings enabled large-scale, single-unit recordings of neural population dynamics across V1 and ACC. We quantified multiple aspects of V1 responses, including response dynamics and orientation selectivity, across control, masking and optogenetic conditions. Preliminary results show that both backward masking and inhibition of ACC to V1 projections reduce the amplitude of the initial stimulus-evoked response (~0-250 ms), predominantly to the preferred orientation. The resulting reduction in orientation selectivity appears stronger during inactivation of ACC feedback onto V1 than during masking. Together, these findings suggest that both visual backward masking and disruption of ACC feedback onto V1 influence early stages of visual processing, and specifically indicate a role for top-down modulation in shaping stimulus selectivity in the visual cortex. However, the effects of masking and of ACC to V1 inhibition are not identical, suggesting that that other pathways may also be involved in determining perceptual experience.

Disclosures: S.C. Gnodde: None. **L. Kroeze:** None. **J.C. Francken:** None. **T. Stein:** None. **U. Olcese:** None.

Poster

PSTR362: Visual Cortex: Functional Architecture and Circuits

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.09/CC1

Topic: E.06. Vision

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Toho University Grant for Research Initiative Program (TUGRIP)

Title: Interactions between fundamental microcircuits involving three inhibitory interneuron classes for the surround suppression in V1

Authors: *N. WAGATSUMA;
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Abstract: The superficial layers of the primary visual cortex (V1), particularly layers 2/3, contain fundamental microcircuits for visual information processing. These microcircuits consist of excitatory pyramidal neurons and three major classes of inhibitory interneurons: parvalbumin-positive (PV), somatostatin-positive (SOM), and vasoactive intestinal polypeptide-positive (VIP) interneurons. Interactions among V1 microcircuits across receptive fields are essential for integrating visual information over extended regions of space, yet the cell-type-specific circuit mechanisms underlying these lateral interactions remain incompletely understood. Here, we developed a biologically plausible computational network model of layer 2/3 V1 comprising pyramidal neurons and PV, SOM, and VIP interneurons to examine how inhibitory interneuron subtypes contribute to interactions between neighboring microcircuits. Model simulations showed that lateral projections from pyramidal neurons in one microcircuit to SOM interneurons in another microcircuit can account for surround suppression and preferentially generate beta-frequency activity at 20-30 Hz, consistent with physiological observations in V1. By contrast, lateral projections mediated by PV interneurons evoked weaker beta- and gamma-frequency activity and failed to reproduce physiologically observed surround modulation. The model further suggested that inter-microcircuit synchrony between pyramidal neurons and SOM interneurons contributes to beta-band activity induced by large visual stimuli. These findings provide a circuit-level mechanism linking receptive-field interactions, surround suppression, and beta-frequency activity in V1, and identify SOM interneurons as key mediators of long-range lateral interactions in cortical microcircuits.

Disclosures: N. Wagatsuma: None.

Poster

PSTR362: Visual Cortex: Functional Architecture and Circuits

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Program #/Poster #: PSTR362.10/CC2

Topic: E.06. Vision

Support: General Foundation for the Tohnetsu Science and Technology

Title: A mathematical model of the formation of species-specific orientation representations in the primary visual cortex

Authors: *N. IKEGAYA, M. MIYASHITA, S. TANAKA;
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Abstract: In the primary visual cortex of monkeys and cats, preferred orientations are arranged along the cortical surface in an orderly manner, forming so-called orientation maps. In contrast, in the rodent visual cortex, preferred orientations are represented irregularly in a salt-and-pepper-like fashion, and only 30-40% of neurons exhibit orientation selectivity. These observations raise a question of why the regularity of orientation maps is so different depending on species. To address this question, we reexamined orientation map formation using computer simulations based on our previously proposed model of activity-dependent rewiring of geniculocortical afferent inputs. We focused on how the orientation representation changes qualitatively as a function of two parameters: the density of intracortical excitatory connections and the initial number of geniculocortical afferent inputs. When the probability that excitatory neurons connect to neighboring neurons is denoted by p, a net balance between excitation and inhibition leads to the weight of each synapse, which is proportional to $1/p$. Using this framework, we conducted simulations in which p and the initial number of afferent inputs served as control parameters. When the initial number of inputs was set to 100 and p=100%, a regular orientation map similar to that observed in monkeys and cats was formed; when the value of p was reduced, the orientation representation became irregular, but nearly all model cortical neurons exhibited orientation selectivity. On the other hand, for low initial number of afferent inputs and low value of p, a salt-and-pepper-like orientation representation was reproduced. These results suggest that species-dependent differences in orientation representation along the visual cortices are caused by the density of excitatory connections and the number of afferent synapses at birth. Our assumptions of the control parameters p and the initial number of afferent inputs are consistent with experimental observations: in rodents, excitatory connections are sparse but strong [Cossell et al., 2016], and the number of synaptic connections at birth is significantly lower than in monkeys [Wildenberg et al., 2023]. In the salt-and-pepper-like orientation representation, many neurons with low orientation selectivity responded to multiple stimulus orientations. We therefore analyzed the temporal changes in the orientation-tuning profiles of these neurons. We found that many neurons exhibited continuous changes in their optimal orientation over time, suggesting that neurons responding to complex visual stimulus patterns already exist in the primary visual cortex of rodents.

Disclosures: N. Ikegaya: None. **M. Miyashita:** None. **S. Tanaka:** None.

Poster

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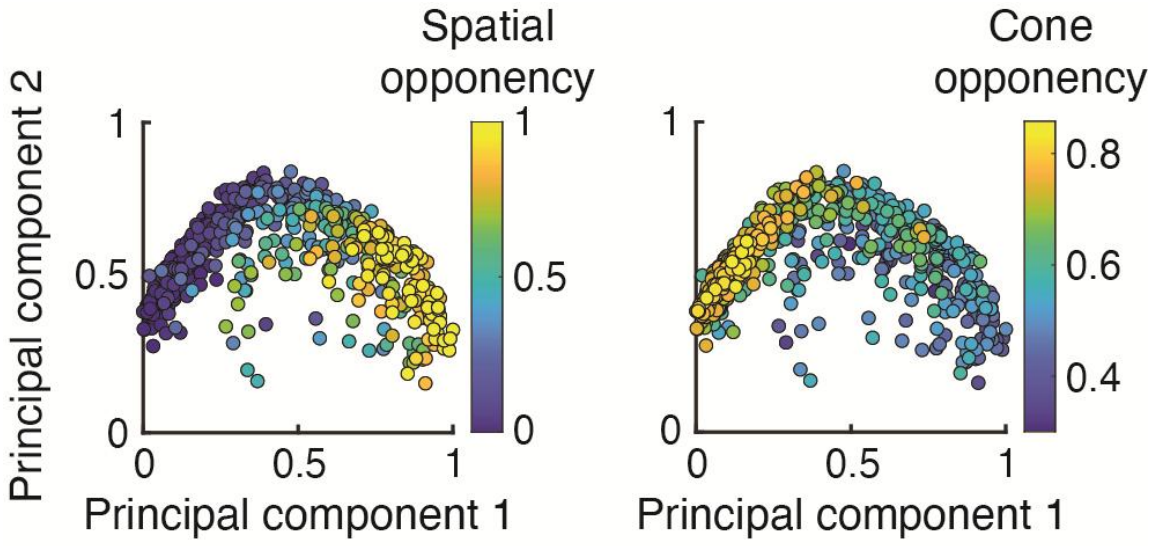
Program #/Poster #: PSTR362.11/Web Only

Topic: E.06. Vision

Title: A model for chromatic and spatial opponency in primary visual cortex

Authors: M. SOMARATNA, ***A. W. FREEMAN**;
Univ. of Sydney, Sydney, Australia

Abstract: INTRODUCTION. Neuronal signals leading to colour vision originate in cone photoreceptors. Signal processing in the retina leads to cone opponency, that is, antagonism between signals from neighbouring cones differing in type. Further processing in primary visual cortex leads to spatial opponency, the antagonism between signals at differing visual field locations. In the primate this spatial processing originates in the input cortical layer, 4Cbeta, but there is considerable uncertainty about spatial opponency in this layer for several reasons. Layer 4Cbeta: is relatively thin, making it less accessible to electrophysiology; is too deep to be reached by conventional intrinsic and calcium imaging; has no cytochrome oxidase blobs, and therefore no anatomical guide to opponency. We sought to learn more about the relationship between cone and spatial opponency in layer 4Cbeta. METHODS. We used a computational model to pursue this aim. The model simulated signals in the foveal midget/parvocellular pathway from cones to layer 4Cbeta of primary cortex in macaques. We used responses to drifting achromatic and equiluminant gratings to calculate indices for both types of opponency; both indices had a range of 0 to 1. RESULTS. Analyses of model responses yielded the following results. 1. All 4Cbeta neurons display some cone opponency. 2. Spatial frequency responses vary from lowpass to bandpass across the population, with a corresponding increase in spatial opponency from 0 to 1. 3. A double opponency index can be calculated by simply multiplying the cone and spatial opponency indices. 4. Spatial and cone opponency are negatively correlated, and we used a principal components analysis to remove the correlation. As shown in the attached figure, the first principal component indicates that neurons lie along a continuum from maximum cone opponency to strongly spatial opponent. CONCLUSION. We suggest that quantifying opponency in empirical data from primary visual cortex can reveal previously unseen relationships between neuronal properties.



Disclosures: M. Somaratna: None. **A.W. Freeman:** None.

Poster

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Topic: E.06. Vision

Support: NIH Grant R01 EY011488

Title: Functional 3-photon imaging of layer 4 neurons in ferret V1 reveals coherent integration of ocular and polarity input streams follows onset of visual experience

Authors: *A. ROY[1], F. WU[1], R. SATTERFIELD[1], J. T. TING[2], D. FITZPATRICK[1];
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Abstract: Layer 4 (L4) of primary visual cortex (V1) is the major target of visual thalamus (LGN) and plays a critical role in building the response properties that distinguish cortical circuits from thalamic inputs. Computations in L4 may underlie the emergence of binocularly-aligned orientation selectivity via synaptic interactions integrating four parallel streams of thalamic inputs that are exclusively driven by the ipsilateral or contralateral eye and respond selectively to positive (ON) vs negative (OFF) luminance changes. However, the extent to which ocular and polarity integration begin at this first stage of cortical processing and how visual experience shapes this process during development is unclear. The lack of suitable expression vectors for L4 in carnivores and the depth limits of 2-photon microscopy have impeded application of *in vivo* optical imaging to study the developmental dynamics in L4. We overcame these obstacles by developing novel enhancers targeting L4 excitatory cells (via collaboration with The Allen Institute for Brain Sciences) and employing 3-photon microscopy to image calcium responses from cells expressing GCaMP under these enhancers at depths inaccessible by 2-photon imaging (>500 um) in ferret V1. In a dataset comprising >3000 imaged cells, we found a robust increase in the fraction of orientation-selective cells in L4 following onset of vision. Our results also indicated that L4 cells are largely monocular with a strong contralateral input bias before eye opening but following 10-20 days of visual experience a substantial fraction of binocular cells with binocularly-matched orientation preferences appear - suggesting rapid experience-driven binocular integration in L4. Furthermore, to investigate the reorganization of polarity inputs in L4 following onset of vision, we mapped the linear receptive fields (RFs) of L4 cells by reverse correlating 3-photon calcium responses to white noise stimuli. Prior to eye opening, most L4 cells featured single-subunit RFs dominated by either ON or OFF responses. Nevertheless, the moderate elongation of these subunits weakly predicted the orientation biases of the cells. In contrast, a greater fraction of cells in experienced animals displayed RFs with segregated ON and OFF subunits that were also more elongated along the axis of preferred orientation. This reshaping of RF structure predicted sharpened orientation tuning following vision that were consistent with the orientation tuning measured from the same cells. Together,

these results identify L4 as a critical site for rapid experience-driven modifications during early development that culminate in mature cortical properties.

Disclosures: A. Roy: None. **F. Wu:** None. **R. Satterfield:** None. **J.T. Ting:** None. **D. Fitzpatrick:** None.

Poster

PSTR362: Visual Cortex: Functional Architecture and Circuits

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Program #/Poster #: PSTR362.13/CC4

Topic: E.06. Vision

Support: NIH Grant EY030550

Title: Synaptic basis for cortical and thalamic information flow across visual processing hierarchies

Authors: M. HALLER, *G. T. NESKE;
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Abstract: Communication among neocortical regions underlies fundamental sensory, motor, and cognitive operations of the brain. Thus, it is essential to determine the synaptic mechanisms by which distinct cortical regions become functionally connected. While direct (i.e. corticocortical) synaptic links between cortical regions have traditionally been considered the dominant mode of cortical functional connectivity, these regions can also influence one another indirectly through transthalamic connections involving the higher-order thalamus, such as the visual pulvinar nucleus. Yet, the distinct synaptic properties of corticocortical connections and their transthalamic counterparts are unclear. Furthermore, we lack any data on the synaptic integration of these two sources of inter-cortical connections. Here, using the mouse visual system as a model, we combine pathway-specific circuit labeling with optogenetic activation of corticocortical and transthalamic pathways to determine their synaptic properties and integration within hierarchically defined regions of the cortex. Combining anterograde transsynaptic labeling with intersectional genetics, we first describe a method to identify higher-order thalamocortical neurons that function in specific transthalamic pathways, which revealed their spatial organization within the pulvinar. Using dual-color optogenetic activation of corticocortical and transthalamic pathways that originate form the same cortical source and terminate in the same cortical target, we find massive monosynaptic convergence of these two pathways onto single cortical neurons, in both feedforward and feedback directions. Additional analysis of the synaptic physiology showed that while corticocortical and transthalamic pathways were comparable in their response magnitude, kinetics, and postsynaptic receptor composition, they differed in their synaptic dynamics, with the transthalamic pathways exhibited more short-term depression than the corresponding corticocortical pathways. Together, these results demonstrate that across multiple visual processing hierarchies, corticocortical and transthalamic

pathways synaptically converge on single neurons, though with distinct dynamics, potentially providing specific windows of opportunity for these two pathways to optimally drive cortical neurons.

Disclosures: M. Haller: None. **G.T. Neske:** None.

Poster

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Topic: E.06. Vision

Support: NIH Grant R01EY011488 (DF)
NIH Grant K99EY034936 (AAL)

Title: Laminar interactions driving binding-by-synchrony and their development in ferret V1

Authors: *A. A. LEMPEL[1], D. FITZPATRICK[2];
[1]Max Planck Inst. Florida, Jupiter, FL; [2]Max Planck Florida Inst., Jupiter, FL

Abstract: A fundamental function of the visual cortex is to integrate local features into coherent perceptual representations. One proposed mechanism is binding by synchrony, whereby neurons responding to different features of the same object exhibit coordinated oscillatory activity. Although synchronized oscillations have been linked to perceptual grouping, sensory integration, and attention, both their circuit origins and computational roles remain debated. A key unanswered question is how cortical synchrony and its relationship to stimulus coherence emerge during development. To address this question, we studied the primary visual cortex of ferrets, a powerful model of visual system development. To characterize the laminar organization of synchronous activity, we grouped multiunit spiking activity according to cortical depth and quantified oscillatory dynamics across development. At eye opening, cortical activity exhibited only low-frequency (~10 Hz) oscillations across all layers. After two weeks of visual experience, robust ~25 Hz oscillations emerged throughout the cortical circuit except in the thalamorecipient layer 4. In mature animals, oscillation frequencies increased further within output layers 2/3 and 5, reaching ~60 Hz. This developmental progression indicates that synchronized oscillations are not an intrinsic feature of cortical responses but instead emerge through experience-dependent circuit refinement. We next tested whether these oscillations depend on stimulus coherence by manipulating the relationship between visual stimuli presented in the receptive-field center and surround. Disrupting center-surround coherence markedly reduced oscillatory synchrony in both juvenile and mature animals, suggesting that synchrony reflects a common cortical computation across development whose temporal dynamics accelerate with maturation. Finally, we investigated the circuit mechanisms underlying synchrony in juvenile animals by testing the contribution of layer 4 inputs. Optogenetic suppression of layer 4 activity reduced response magnitude in layer 2/3, yet responses that persisted in layers 2/3, 5, and 6 remained strongly

orientation selective. In contrast, oscillatory synchrony was profoundly disrupted in all those layers. These findings reveal a dissociation between stimulus selectivity and synchrony, indicating that the synchrony code for stimulus coherence depends critically on developing interactions between layer 4 and the rest of the cortical circuit. Future work will determine how these interactions contribute to the emergence of mature 60 Hz oscillations and cortical binding mechanisms.

Disclosures: A.A. Lempel: None. **D. Fitzpatrick:** None.

Poster

PSTR362: Visual Cortex: Functional Architecture and Circuits

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Program #/Poster #: PSTR362.15/CC6

Topic: E.06. Vision

Support: NSF grant 2313149
SRC/Jump2 CoCoSys

Title: Toward a mechanistic understanding of inference in visual cortex and diffusion models

Authors: *Z. YUN[1,2], A. BELSTEN[1,3], Z. KADKHODAIE[5,6], D. BI[1,2], Y. CHEN[7], B. A. OLSHAUSEN[1,3,4];
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Abstract: We describe a model of perceptual inference in primary visual cortex (V1) equivalent to a minimal diffusion model whose function can be readily understood from its parameters. The model is based on sparse coding with a non-factorial prior over latent variables in the form of an unconstrained, pairwise interaction matrix, extending standard sparse coding inference to a general recurrent dynamical system. We efficiently train these recurrent dynamics using a denoising score-matching objective and implicit differentiation. After training on natural images, the learned interaction matrix mirrors the structure of horizontal connections in superficial layers of V1 that link neurons of similar orientation tuning. This model exhibits exceptionally good denoising performance, restoring image features such as extended contours amid extreme visual ambiguity, nearly matching the behavior of standard, black-box diffusion architectures in generalization regime. Owing to the model's simplicity, the network’s Jacobian can be decomposed directly in terms of the interaction matrix between latent variables, revealing mechanistically how the recurrent dynamics assign high probability over a continuous family of natural structural deformations. Intriguingly, within this circuit, a large fraction of latent variables learn to disconnect from visual input altogether, essentially forming a hierarchical representation that appears to enforce global consistency among image features. Together, the model and results bridge two distinct domains: for neuroscience, it generates concrete, testable

hypotheses regarding functional connectivity in recurrent neural circuits during perceptual inference tasks; for machine learning, it elucidates the internal mechanisms learned by diffusion models that allow them to generate infinitely many novel images from a finite training set.

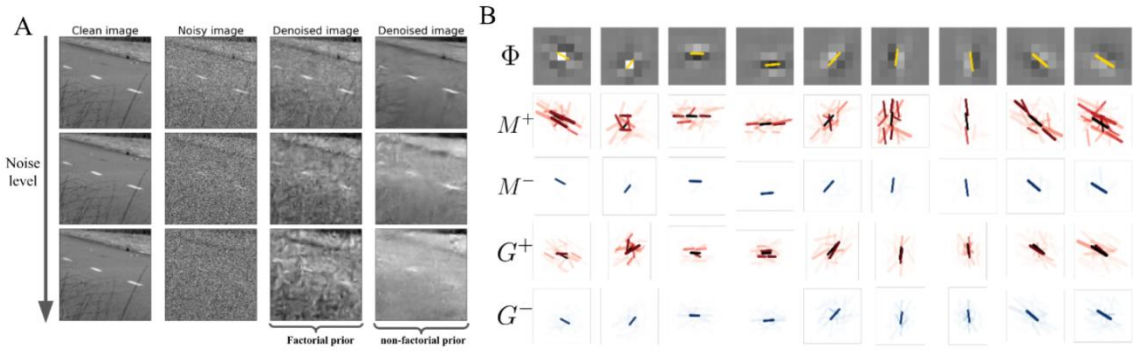


Figure 2: **Emergence of V1-like connectivity and denoising performance. (A)** Denoising comparison across increasing noise levels (rows) showing clean, noisy, factorial, and non-factorial reconstructions. **(B)** Visualization of learned latent interactions for a subset of dictionary elements. Each column is centered on one reference basis function Φ_i shown in the top row. The yellow/black bar indicates its position and preferred orientation. Rows below show needle plots of its interactions with other basis functions Φ_j: excitatory and inhibitory components of the learned pairwise matrix M_{ij}, followed by excitatory and inhibitory components of the Gram matrix $G_{ij} = \Phi_i^\top \Phi_j$. Each colored bar is placed at the spatial location and orientation of Φ_j, and color saturation indicates interaction magnitude.

Disclosures: Z. Yun: None. **A. Belsten:** None. **Z. Kadkhodaie:** None. **D. Bi:** None. **Y. Chen:** None. **B.A. Olshausen:** None.

Poster

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STI2030-Major Projects Grant 2022ZD0204600
National Natural Science Foundation of China Excellent Young Scientists Fund Grant 31625012

Title: Orientation pinwheels in primate V1: a comparison between intrinsic signal optical imaging and two-photon calcium imaging

Authors: *Z. DAI[1], R. ZHANG[1], J. WANG[1], G. WANG[2], H. D. LU[2];
[1]State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China;

[2]Dept. of Neurology, Zhongshan Hospital, Inst. for Translational Brain Res., Fudan Univ., Shanghai, China

Abstract: Orientation preference maps in primate V1 exhibit pinwheel-like structures. These structures are typically characterized using intrinsic signal optical imaging (ISOI), which relies on indirect hemodynamic signals and involves spatial filtering during data processing. However, whether ISOI-identified pinwheels truly reflect the orderly organization of orientation-selective neurons has been questioned. Here, we examined 31 pinwheels across 5 animals (4 *Macaca mulatta* and 1 *Macaca fascicularis*) using both ISOI and two-photon calcium imaging (2P imaging) at matched cortical sites. By comparing pinwheel center locations, orientation preference distributions, and map topology, we found that approximately 65% (20/31) of the ISOI pinwheels had corresponding pinwheel structures in their matched 2P maps. For the remaining ISOI pinwheels (11/31), either the ISOI map or the 2P map exhibited low local signal-to-noise ratios, which may have affected the correspondence. Moreover, ISOI pinwheels located in high signal-to-noise regions tended to lie closer to ocular dominance centerlines and color blobs, suggesting that local signal quality may also influence estimates of spatial relationships between pinwheels and other functional structures. Together, our findings demonstrate that the majority of ISOI pinwheels can be confirmed at the neuronal level, whereas those that cannot be confirmed are likely associated with poor imaging quality.

Disclosures: Z. Dai: None. **R. Zhang:** None. **J. Wang:** None. **G. Wang:** None. **H.D. Lu:** None.

Poster

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Program #/Poster #: PSTR362.17/CC8

Topic: E.06. Vision

Support: DFG Projekt 425899996 (SFB 1436)
DFG (KR 4062/5-1)
DFG Projekt 498049560

Title: Alignment of direction- and disparity-columns in macaque V5/MT revealed with high-density Neuropixels probes

Authors: *A. ADDLESEE[1,3], H. SUYAMA[1], K. TEH[1], A. J. PARKER[4,1,3], J. KREMKOW[1], K. KRUG[2,4,3];
[2]Sensory Physiol., [1]Otto-von-Guericke Univ. Magdeburg, Magdeburg, Germany; [3]Leibniz Inst. for Neurobio., Magdeburg, Germany; [4]Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom

Abstract: Columns of direction- and binocular disparity-selective neurons in macaque area V5/MT have been inferred from recordings with single electrodes. However, their detailed spatial pattern and relationship to one another are unclear. We conducted simultaneous

recordings of neuronal activity across layers and columns of V5/MT from two Rhesus monkeys (*Macaca mulatta*), using high-density Neuropixels electrodes (Imec, 1.0 NHP Long, electrode spacing 20 µm in two columns, 125 µm apart). Recording chambers over left hemisphere, angled at 22° above horizontal, allowed a posterior approach through visual cortex to layers 6 to 1 of extrastriate visual area V5/MT. During recordings, monkeys maintained fixation while dynamic random dot stimuli were shown. The stimuli were positioned over the multi-unit (MU) activity receptive field for the recorded site, later confirmed in offline analysis. We systematically varied (i) direction of motion (0°, 60°, 120°, 180°, 240°, & 300°) or (ii) the binocular disparity (±0.6°, ±0.4°, ±0.2°, ±0.1°, ±0.05° & 0°) of the dots. Kilosort4, Bombcell, and Phy2 provided automatic and manual curation of single-unit (SU) activity. MU activity was extracted from bandpass filtered, common average referenced signals, with a channel threshold of at 4x sd above noise. Disparity and direction tuning curves (ANOVA $p>0.05$) for MU and SU were fitted for each significant cluster. These plots confirmed a clear topographic progression of direction preference along the electrode length, interrupted by regular 180° changes, and an alignment of the SU preferences to local MU activity. We estimate that preferred motion direction changes systematically in V5/MT with a maximal rate of change of 310-550°/mm, close to that reported by Albright et al (1984). In both animals, we also found more extended regions of cortex, spanning several 100 µm, where the preferred motion direction at neighboring channels was closely similar. Analysis of MU and SU disparity preferences revealed that disparity selectivity is organised in discrete spatial clusters with a specific binocular disparity preference ('near' or 'far') over often 200-400 µm. There were also large sections of cortex where disparity selectivity was mixed or absent. Disparity-tuned clusters were usually present within direction-tuned regions. Regions with slowly changing, aligned direction and disparity tuning, form clusters of selectivity within V5/MT for specific conjunctions of direction of motion and 3D depth. This architecture could underpin the neural substrate for stable structure-from-motion perception.

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Poster

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Title: Cell-type-specific contributions to object representations in macaque inferior temporal cortex and artificial neural networks

Authors: *S. MUZELLEC[1], K. KAR[2];
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Abstract: How do excitatory and inhibitory neurons contribute to object representations in primate inferior temporal cortex? We recorded population activity with Utah arrays from three macaques viewing 640 images from 8 object categories and classified neurons as putative excitatory (n=162) or inhibitory (n=31) using spike waveform clustering. We first asked when each population begins to carry object information. Inhibitory neurons exhibited reliable responses earlier than excitatory neurons (mean latency: Inh=87 ms, Exc=117 ms; $p<0.001$), suggesting that inhibitory populations participate in the earliest feedforward sweep. However, these responses differed markedly in format: inhibitory neurons showed greater across-image variance ($p<0.001$), but lower stimulus selectivity ($p=0.002$) and category selectivity ($p<0.001$), indicating distinct representational trajectories. We next tested whether these differences matter for categorization. Excitatory populations achieved higher category decoding accuracy than inhibitory populations ($p<0.001$). Consistently, when varying the excitatory/inhibitory ratio while keeping population size fixed, the highest decoding accuracy was obtained from populations containing only excitatory neurons. Excitatory activity also aligned more strongly with monkeys' image-by-image recognition accuracy (70-170 ms: $\Delta=7\%$, $p<0.001$), indicating that excitatory neurons better capture which images are easy or difficult for the animal. To understand why inhibitory neurons show higher response variance yet lower decoding accuracy, we examined representational geometry. During the 70-170 ms window, inhibitory responses formed a correlated, high-radius manifold with limited category separation. In contrast, excitatory responses compressed into lower-radius and more separated manifolds, consistent with a stronger role in object categorization. Finally, we asked how these cell-type-specific representations relate to artificial vision models. Standard feedforward ANNs (i.e., ResNet-18) predicted excitatory responses better than inhibitory responses ($p<0.001$), suggesting that object-optimized models preferentially approximate excitatory projection populations while failing to capture inhibitory computations. To address this limitation, we built ANNs with explicit cell-type constraints, in which units are constrained to be excitatory or inhibitory. These biologically constrained ANNs provide a framework for mapping ANN cell types onto neural cell types and testing how excitatory and inhibitory computations jointly shape object recognition in brains and models.

Disclosures: S. Muzellec: None. **K. Kar:** None.

Poster

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Title: Dissociation between neural representation of local and global scene segmentation cues

Authors: *A. DAS, M. AZADI, F. DIDEHVAR, T. P. FRANKEN;
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Abstract: To make sense of the world around us, the visual system must segment complex visual scenes into an organized representation of distinct object surfaces. Scene segmentation signals are prominent in the primate visual cortex. A substantial proportion of neurons in visual cortical Areas V2 and V4 signal border ownership, i.e. which side of a border is owned by a foreground surface. Psychophysics studies suggest that scene segmentation is informed by cues such as contour junctions. A prominent type of contour junction is the T-junction, which is formed where a border of an occluded surface meets that of an occluding surface. The resulting 'T' shape is informative about the depth order of the surfaces: the stem of the T points away from the occluding surface. How the visual system represents T-junctions and how these signals relate to the neural representation of border ownership remains poorly understood. Here we investigate this question by directly comparing the neural representation for border ownership and for T-junction orientation. We recorded spike rates from single and multi-units in visual areas V4 and V2 using Neuropixels probes in a male macaque. After measuring the classical receptive fields (cRFs) of the neurons, we presented three types of scenes during passive fixation. First, classical border ownership scenes, in which the cRFs only contained a luminance border which could be owned by a square surface on one or the other side (Square scenes). Second, scenes in which the cRFs only contained an isolated T-junction (Tj-cropped). Third, stimuli in which identical T-junctions as in Tj-cropped scenes were part of a more elaborate scene (a pair of occluding squares; Tj-squares). Each type of scene was presented at 8-12 orientations, and with different possibilities for the contrast polarity across the borders in the scene. We find that a substantial proportion of units are tuned to the orientation of T-junctions in Tj-cropped scenes. We find that the tuning for T-junction orientation is significantly correlated between Tj-cropped and Tj-squares scenes for V2 units, but not for V4 units. In contrast, in V4, and also in V2, we find a significant correlation between the preferred orientation of border ownership between Square scenes and Tj-squares scenes. In neither area we find a significant correlation between the tuning for T-junction orientation in Tj-cropped scenes and border ownership tuning in Square scenes. Together, our data suggest a dissociation in the representation of local and global scene segmentation cues, with a shift in dominance from a more local to a more global representation between V2 and V4.

Disclosures: A. Das: None. **M. Azadi:** None. **F. Didehvar:** None. **T.P. Franken:** None.

Poster

PSTR362: Visual Cortex: Functional Architecture and Circuits

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Title: Spatiotemporal Continuity Shapes Information Flow in the Primate Ventral Stream

Authors: Y. XUE[1], A. G. SHEFFIELD[2], M. P. JADI[3], ***A. S. NANDY**[4];
[1]Electrical Engin. & Psychiatry, [2]Neurosci. & Psychiatry, [3]Psychiatry & Neurosci., [4]Neurosci. & Psychology, Yale Univ., New Haven, CT

Abstract: Recurrent interactions between cortical areas are thought to be critical for coherent perception, yet how these long-range pathways depend on the spatiotemporal structure of natural vision remains unclear. We tested whether disrupting spatiotemporal continuity selectively impairs inter-areal communication in the ventral visual stream. We recorded simultaneously across cortical layers in areas V2 and V4 of awake marmosets (n=2) using laminar electrode arrays during free viewing. Animals watched intact movies or temporally shuffled versions in which consecutive 120-ms segments were randomly reordered, preserving local visual statistics while disrupting long-timescale spatiotemporal relationships. Spike-triggered current source density confirmed functional connectivity between recording sites. We quantified inter-areal communication using spike-field phase consistency, probabilistic graphical models (Multi-Timelag weighted Dynamic Bayesian Networks), and reduced-rank regression to characterize communication subspace geometry. Temporal shuffling exerted minimal effects on oculomotor behavior, firing rates, and population dimensionality, ruling out gross state differences as explanations for neural effects. However, inter-areal coordination was profoundly disrupted. Spike-field coupling decreased across theta frequencies in feedforward (V2→V4) and alpha/low-beta frequencies in feedback (V4→V2) directions. Critically, directed spiking dependencies revealed an asymmetric effect: feedback connections from deep-layer V4 to superficial V2 were selectively weakened, while feedforward dependencies remained intact. Subspace analyses showed that temporal discontinuity both rotated and destabilized the low-dimensional communication channels linking V2 and V4, reducing predictive accuracy and increasing geometric variability. In contrast, within-area laminar communication was largely preserved across conditions. These findings demonstrate a clear dissociation between local and long-range processing in the ventral stream. While local circuits can represent short-timescale visual information relatively independently, coherent coordination across hierarchical levels, particularly through feedback pathways, depends critically on the continuous spatiotemporal structure characteristic of natural vision.

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Poster

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Program #/Poster #: PSTR362.21/CC12

Topic: E.06. Vision

Title: Translational Invariance in Early Convolutional Units

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Abstract: Visual recognition remains stable despite changes in object position, scale, viewpoint, and illumination. This stability is commonly attributed to an intrinsic capacity of neuronal representations to preserve stimulus selectivity across transformations, putatively emerging through mechanisms such as pooling, increasing receptive fields, recurrent processing, hierarchical feature abstraction and learning-dependent processes. However, it remains unclear to what extent invariance reflects specialized mechanisms rather than simple consequences of stimulus structure and feature-detector selectivity: for example, when the local image pattern that drives a neuron is preserved or reappears across the image space. Here, we examined whether response stability across image translations can be observed in the absence of these higher-order mechanisms by analyzing the first convolutional layer (Conv1) of deep neural networks, including AlexNet, ResNet50, and EfficientNet-B0. These layers lack all mechanisms commonly invoked to explain invariance including pooling and recurrence. Each unit operates as a local feature detector by comparing a local image patch to a fixed filter. For each Conv1 unit, we measured responses to natural images translated across pixel positions and quantified invariance as the preservation of image preference rankings across translations. Under this definition, a unit is considered “invariant” when preferred stimuli remains preferred despite changes in image position. Surprisingly, “invariance” was frequently present in first-layer units. In AlexNet, invariance scores ranged from 0.21 to 0.93 (mean = 0.52), with more than half of all units exhibiting correlations greater than 0.5 (N = 51). Similar distributions were observed in ResNet50 and EfficientNet-B0, indicating that response stability is not unique to a single architecture. Conv1 units lack pooling, recurrent interactions, lateral computations, and hierarchical feature abstractions; thus, these findings demonstrate that some invariance arises from the interaction between a natural image and a local fixed convolutional filter. The results suggest that response stability does not necessarily require specialized invariance-generating mechanisms, motivating a comprehensive reexamination of how transformation tolerance is measured and interpreted in both biological and artificial visual systems. Ongoing experiments in our laboratory are extending this framework to in vivo neuronal recordings from V1, V4, inferotemporal cortex (IT), and pulvinar to reveal the accurate extent of single-neuron and single-column invariance across the visual system.

Disclosures: M.A. Berkelaar: None. **C.R. Ponce:** None.

Poster

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Title: Functional Connectivity of the Foveolar Core in Primate Visual Cortex

Authors: *F. TIAN[1,2], M. CHEN[1], M. QIAN[3], G. PAN[1,2], A. W. ROE[3,4];
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Abstract: Motivation: The primate visual system contains classical organization, with early visual cortical areas V1-V4 defined by visual retinotopy and functionally segregated parallel processing streams; these several retinotopies converged at the foveal confluence. However, recent ultrahigh field fMRI revealed that the confluence comprises a complex of multiple (8) foveolar loci (one at each of dorsal and ventral V1/V2, V2/V3, V3/V4, V4/TEO) which surround a central non-visuotopic area called the *foveolar core* (Qian 2025 Nature Neurosci). Here, we examined the functional connectivity of the core using pulsed infrared neural stimulation in ultrahigh field MRI (INS-fMRI).**Methods:** In 3 anesthetized and paralyzed (to prevent eye drift) macaques, we determined the location of foveolar loci by mapping the intersection of the vertical (VM) and horizontal (HM) meridia. A 0.2° square patch was then presented at the foveolar center, which induced activation of 8 foveolar loci in each hemisphere; the region encircled by these 8 loci identified the core. Using 200μm optical fibers, we delivered 1875nm INS stimulation while imaging in 7T MRI (1mm isotropic, whole brain). Significant activations across the brain were identified via GLM ($p<0.001$, FDR corrected).**Results:** In 3 monkeys, INS stimulation at single sites in the foveolar core evoked activations across multiple higher-order visual areas in the dorsal, ventral, motion/social, and dorsomedial pathways. Unlike V2 stripe stimulation which produced expected pathway-specific responses (Tian et al, Soc for Neurosci 2025), single site foveolar core stimulation simultaneously engaged both 2 or more pathways, indicating a divergent projection pattern. Moreover, unilateral stimulation of the foveolar core reliably evoked focal activation in the visual periphery, in the contralateral foveolar core (suggesting the presence of coordinated callosal connections linking homologous foveolar regions), as well as in contralateral visual pathways.**Conclusion:** Our findings suggest the foveolar core is unlike the classical areas of occipital visual cortex. Instead, the core appears to function as an integrative, bilaterally coordinated hub that distributes complex visual information (high spatial frequency, motion dot patterns, color, large stimulus preference) across multiple processing streams. This specialized architecture may support rapid and coherent processing of foveolar vision for different behavioral goals in primate looking behavior.

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Poster

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Topic: E.06. Vision

Support: EY026568
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EY003611

Title: Anatomical changes in V1 are correlated with functional deficits in deprivation amblyopia NHP models

Authors: *Z. ZEHRA[1], R. J. KWAW[1], H. MENG[1], K. BEACH[1], R. SAH[1], L. OSTRIN[1], N. PATEL[1], K. DUFFY[2], V. DAS[1];
[1]Col. of Optometry, Univ. of Houston, Houston, TX; [2]Dalhousie Univ., Halifax, NS, Canada

Abstract: Purpose: Animals reared with monocular deprivation (MD) undergo anatomical remodeling in the lateral geniculate nucleus (LGN) and primary visual cortex (V1). Functionally, these animals also have reduced visually evoked potentials (VEP) measured through the deprived eye. The purpose of this study was to compare the magnitude of anatomical deficits in the LGN and V1 and how they relate to VEP measurements in rhesus monkeys subjected to MD. Methods: Infant monkeys (n=5) were monocularly deprived using LP Bangerter foils for ~20 weeks. Following MD, VEP responses were measured to assess visual cortical responsivity using phase reversing (6 Hz) vertical square wave gratings (0.25 - 16 cyc/deg). All animals were then perfused-fixed. The LGN and V1 tissue sections (40 μm) were labeled for neurofilament protein (NF) and stained for Nissl substance, followed by imaging and analysis. Within V1, ocular dominance column (ODC) width was measured along with NF positive (NF+) cell density within ODCs and LGN layers serving the deprived and non-deprived eyes. Nissl-stained sections were used to quantify neuron soma-size in the deprived and non-deprived LGN layers. Ocular dominance indices (ODI) were calculated from VEP responses and each neuroanatomical metric as the difference in measurements between both eyes divided by their sum. Mann Whitney U test and Wilcoxon rank sum test were performed to compare deprived and non-deprived regions, and a Spearman correlation test was applied to test the correlation of VEP ODI with the ODI derived from histological measurements. Results: The presence of amblyopia was confirmed by a marked reduction of VEP responses measured through the deprived eye. Anatomically, animals with the largest amblyopic deficit, as determined by the VEP, showed a clear ODC striped pattern within V1. NF+ cell density and ODC widths were reduced in columns serving the deprived eye compared to non-deprived eye. Similarly, NF+ cell density and average neuron soma-size also show reduction in LGN layers serving the deprived eye. Neuroanatomic ODI values indicated that the magnitude of deficits within V1 was more pronounced than in the LGN.

Moreover, the interocular imbalance estimated via the VEP was larger than the imbalance measured structurally in V1 and LGN. Physiological deficits measured via the VEP were best correlated with the loss of NF+ cell density (r_s=0.6) and ODC width (r_s=0.8) in V1. Conclusion: In form deprivation amblyopic monkeys, functional deficits were correlated with structural deficits in V1 but not in the LGN. It remains to be determined, in this model, whether amblyopia treatments will lead to recovery of structure as well as function.

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Poster

PSTR362: Visual Cortex: Functional Architecture and Circuits

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Title: Image-specific dependence on hierarchical processing during primate object recognition

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Abstract: Real-world objects vary widely in appearance, yet humans and non-human primates recognize them within a single fixation, a behavior known as core object recognition. This ability

depends on the ventral visual stream, often modeled as a feedforward hierarchy in which object identity emerges from early visual areas to inferior temporal cortex. However, bypass pathways can route information around intermediate stages, raising a key question: is V4 an obligatory bottleneck for all object images, or can some images be recognized from representations available before V4 or partly independent of it? We quantified image-level object discriminability across ventral stream-aligned layers of multiple pretrained artificial neural networks using linear decoding probes. For each image, we computed a slope metric capturing how much decoding improved across the hierarchy, classifying images as low-slope, or early-decodable, versus high-slope, or hierarchy-dependent. We then simulated intermediate-stage disruption by spatially perturbing a V4-like AlexNet layer based on overlap with a macaque V4 population receptive field. This separated deficits due to receptive-field overlap from those due to image-level hierarchical dependence. Mean decoding accuracy increased across stages, but images varied substantially: some were decoded from early layers, whereas others required deeper representations. Slope values generalized across architectures and image sets, while randomized controls produced near-zero correlations. Perturbing V4-like units caused larger impairments for images whose objects overlapped the perturbed receptive field. Within overlapping images, we then tested whether deficits differed between low- and high-slope images. A serial feedforward model predicts similar impairment once object-relevant V4-like units are disrupted. In contrast, a bypass/readout account predicts greater resistance for low-slope images because object identity is already decodable from earlier representations. Thus, this comparison tests whether hierarchical dependence predicts perturbation sensitivity beyond receptive-field overlap alone. In parallel, we established inhibitory DREADD-mediated suppression of macaque V4 during object recognition. Chemogenetic suppression reduced stimulus-evoked V4 activity, altered downstream IT responses, and produced receptive-field-dependent behavioral impairments. Together, these findings identify image classes with different hierarchical dependence and establish a framework for testing whether V4-disruption deficits reflect serial feedforward processing or bypass-supported recognition.

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Poster

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National Natural Science Foundation of China 32271079
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Title: Prioritized representation of different visual features in macaque V2

Authors: *W. ZHAO[1], R. TANG[2], Z. DAI[1], R. ZHANG[1], H. D. LU[3];
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Abstract: Primate V2 is characterized by 3 types of cytochrome oxidase stripes, which are believed to underlie parallel visual processing. However, it remains unclear how visual processing differs across these stripes. With two-photon calcium imaging, we characterized responses of thousands of V2 neurons to chromatic grating stimuli in anesthetized macaques. We confirmed that neurons exhibit various degrees of selectivity for both color and orientation features, but there is a clear emphasis in different stripes: color is the major selectivity for thin-stripe neurons, whereas orientation is the major selectivity for thick- and pale-stripe neurons. Compared with minor selectivity, major selectivity shows stronger tuning, higher consistency, and more robust spatial clustering. Minor features are combined with major ones in an unstructured manner across the cortical surface and feature space. Thus, V2 neurons encode multiple features asymmetrically and the stripes exhibit fundamental cellular-level differences, and parallel processing in the visual pathway is achieved through differential prioritization.

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Poster

PSTR363: Visual System: Plasticity

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Topic: E.06. Vision

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Title: The circuit mechanisms underlying experience-dependent visual plasticity in mouse anterior cingulate cortex

Authors: *A. MALCI[1], J. KINNAMAN[1], R. HERRERA-MOLINA[2], M. S. SIDOROV[1];
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Abstract: The anterior cingulate cortex (ACC) is a prefrontal brain area involved in a wide range of functions including cognitive control, attention and prediction. ACC responds to visual stimuli and is reciprocally connected with visual cortex. Our latest work demonstrated that repeated exposure to a familiar visual stimulus induces stimulus-specific response plasticity in timing (SRPT) of mouse ACC responses in mice. However, the circuit mechanisms of ACC SRPT and how ACC neuronal subpopulations respond and adapt to visual stimuli are yet to be understood. Here, we seek to understand local circuit mechanisms responsible for visual encoding and experience-dependent plasticity in mouse ACC. Using acute high-density electrophysiological recordings in mice, we found that visual stimulation robustly increased

ACC firing rates relative to baseline and elicited sustained post-stimulation firing. During stimulus presentation, ACC neurons exhibit a reduction in firing rates across stimulus blocks, indicative of short-term adaptation. Both wide-spiking (WS) and fast-spiking (FS) ACC neurons are visually responsive. Visual training with familiar stimuli resulted in increased ACC firing rates, while responses to novel stimuli showed smaller changes in firing rate, highlighting the importance of visual familiarity. Together, these results provide insights into local characteristics by which ACC itself encodes visual input. This work may also help to better understand sensory deficits and ACC impairments observed in mouse models of neurodevelopmental disorders. Our ongoing work investigates spontaneous and visually-evoked activity of individual ACC neurons in a mouse model of the neurodevelopmental disorder Angelman syndrome.

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Poster

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Title: Defining the temporal and molecular limits of neural circuit recovery following gene therapy in retinitis pigmentosa

Authors: *K. MILEJCZYK[1], W. LEE[1], M. RASPER[1], M. SCALABRINO[2];
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Abstract: Gene replacement therapy for neurodegenerative diseases slows progression but fails to halt cell death. In the *Cngb1*$^{neo/neo}$ mouse model of retinitis pigmentosa, we previously demonstrated that tamoxifen-inducible genetic rescue of all remaining rods does not prevent continued cell loss, and that late intervention impairs visual recovery. These findings indicate a biological problem beyond gene delivery. *We hypothesize treated photoreceptors retain impaired molecular pathways that contribute to their eventual death.* To test this, we performed electroretinography, optical coherence tomography, histology, and single-cell RNA sequencing (scRNA-seq, 10x FLEX GEN X) of enriched PRs across two rescue paradigms differing in disease stage and rescue extent: 1) partial rescue at early disease, mimicking mosaic viral vector delivery, and 2) full rescue of remaining rods at late disease. Mice of both sexes were used and controls included heterozygous cre-negative and homozygous cre-negative littermates. Retinas undergo papain dissociation, surface antigen-based PR enrichment, and 10x FLEX GEN-X

probe-based sequencing for sample multiplexing across timepoints. Retinal structure and function are assessed longitudinally by OCT and ERG. Early rescue at P30 restored scotopic b-wave amplitudes to wild-type levels within 7 days, demonstrating that the degenerating retina retains robust synaptic plasticity in early disease. In contrast, late rescue at P90 yielded only partial functional recovery with attenuated b-wave amplitudes, suggesting circuit remodeling impairs reconnection. Transcriptomic analysis using a computational manifold to preserves multi-dimensional gene relationships is ongoing to identify co-regulated networks distinguishing surviving from dying PRs after rescue. These findings define a critical period for circuit recovery following gene therapy and identify molecular targets for combination therapies to extend the therapeutic window, with broad implications for neurodegenerative diseases where synaptic remodeling limits regenerative strategies.

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Poster

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Title: Balanced Neurogranin-PP2B Signaling Is Required for Experience-Dependent Synapse Maturation in Visual Cortex

Authors: *M. B. WIGGINS, R. GARCIA, S. N. MOSTOFA, M. T. KLINGHOFFER, A. J. ETINGOF, F. S. HAYDEN, Y. SHEN, J. MOSCHELLA, W. XU;
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Abstract: Neurogranin (Ng) regulates Ca^{2+}/calmodulin (CaM) availability in dendritic spines, shifting the balance between CaMKII-dependent LTP and PP2B (calcineurin)-dependent LTD during the visual critical period. Ng knockdown exaggerates experience-dependent spine loss, implicating elevated PP2B activity as the downstream mediator. We tested this directly using AAV-mediated bidirectional manipulation of Ng and PP2B in layer II/III pyramidal neurons of the primary visual cortex (V1B) during the critical period. Four viral conditions were compared: shLuc/CNAIDScr (control), shNg/CNAIDScr (Ng knockdown), shLuc/CNAID (PP2B inhibition via calcineurin autoinhibitory domain peptide), and shNg/CNAID (combined). Spine density, silent synapse proportion, AMPA/NMDA ratio, and mEPSC frequency were measured at P28-P30 in male and female mice; viral constructs were blinded throughout imaging and analysis. Ng knockdown significantly reduced spine density ($p=0.021$) and elevated silent synapse proportion with reduced AMPA/NMDA ratio ($p<0.0001$), consistent with impaired synapse maturation. PP2B inhibition combined with Ng knockdown rescued spine density to control levels ($p=0.026$

vs. Ng KD; p=0.959 vs. control) and restored silent synapse proportion and AMPA/NMDA ratio, demonstrating that excess PP2B activity mediates Ng knockdown-induced synaptic deficits. Unexpectedly, PP2B inhibition alone also significantly reduced spine density (p=0.024) and elevated silent synapse proportion, indicating that basal PP2B activity is required for normal spine maintenance. Two-way ANOVA revealed a significant interaction between Ng and PP2B manipulations (p<0.0001), demonstrating that the effect of PP2B inhibition on spine stability is contingent on Ng levels. mEPSC frequency trended toward rescue with PP2B inhibition under Ng knockdown conditions, consistent with structural and functional recovery. In dissociated cortical neurons, chemLTP induction (glycine/bicuculline) increased PKA S99 phosphorylation in controls; Ng knockdown abolished this increase, which was rescued by co-expression of CNAID, while CNAID alone modestly blunted the chemLTP-induced PKA S99 phosphorylation ratio, consistent with Ng-PP2B balance regulating the signaling cascade correlating synaptic strengthening. These results establish that precise titration of the Ng-PP2B axis, rather than simple suppression of PP2B, is required for experience-dependent maturation of excitatory synapses during the critical period.

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Poster

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Title: Cyclin-dependent kinase-like 5 (CDKL5) mutant mice display normal binocular depth perception, visual acuity, and other benchmarks of visual cortical function and plasticity

Authors: K. BARBER[1], H. MA[1], T. C. BROWN[1], *A. W. MCGEE[2];
[1]Translational Neurosciences, [2]Univ. of Arizona Col. of Med., Phoenix, AZ

Abstract: Mutations in cyclin-dependent kinase-like 5 (CDKL5) cause CDKL5 deficiency disorder (CDD), a rare form of developmental epileptic encephalopathy that is often co-morbid with central visual impairment (CVI). We investigated whether CDKL5 knock-out (KO) mice may serve as a useful model for CVI although these mice do not display the early onset and often severe seizures that are characteristic symptoms of CDD. We measured motor learning and performance with the rotarod, binocular depth perception with the pole descent cliff task, and visual acuity with the visual water task. Consistent with previous reports, CDKL5 KO mice were hypoactive but their performance on the rotarod was within the range of wild-type (WT) mice. CDKL5 KO mice displayed normal binocular depth perception and visual acuity. These findings

contrast with the impaired depth perception and acuity that we observe with an early postnatal hypoxia model of CVI. Two cytoarchitectural markers of maturation in visual cortex, myelination and perineuronal nets, were also unremarkable in CDKL5 KO mice. Planned experiments include measurements of ocular dominance plasticity with multi-unit recordings and orientation/spatial frequency tuning with calcium imaging at cellular resolution. Updated results will be presented.

Disclosures: K. Barber: None. **H. Ma:** None. **T.C. Brown:** None. **A.W. McGee:** None.

Poster

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Title: Rapid prey capture learning resets V1 activity set points in vivo through homeostatic plasticity mechanisms

Authors: *D. P. LEMAN[1,2], B. A. CARY[2], B. J. LANE[2], D. BISSEN[2], W. WEN[2], N. F. WONG[2], K. BHUT[2], R. SHANLEY[2], G. TURRIGIANO[2];
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Abstract: Neocortical neurons possess stable firing rates to which they faithfully return after sensory perturbations. These activity set points are established early in development and are stable through adulthood, suggesting they are an immutable feature of cortical networks. Here we challenge this idea using an ethological vision-dependent prey capture learning paradigm in juvenile rats. We employed a combination of behavioral analysis, chemogenetics, in vivo electrophysiology, ex vivo slice electrophysiology, and pharmacology to probe how naturalistic learning affects V1 setpoints. We find that rapid prey capture learning required visual cortex (V1) and enhanced the tuning of V1b neurons to specific pursuit epochs across learning sessions. Chronic electrophysiology recordings revealed a slow, state-dependent increase in V1b firing rates that began after learning was complete and persisted for days. This upward firing rate plasticity was gradual, gated by wake states, and accompanied by a TNFα-dependent increase in V1b excitatory activity - all features of homeostatic plasticity within V1. Finally, blocking TNFα signaling after learning reduced the retention of hunting skills and decreased learning-induced changes in V1b activity. Therefore, our findings demonstrate that prey capture learning can modify firing rate setpoints in the visual critical period and support the idea that homeostatic mechanisms can guide and stabilize V1b plasticity underlying the retention of learned visuomotor skills. Our results here reveal that naturalistic behaviors can drive dramatic,

persistent changes in V1b neurons and illuminate a role for homeostatic plasticity mechanisms in consolidating and encoding learning-driven changes in cortical networks.

Disclosures: D.P. Leman: None. **B.A. Cary:** None. **B.J. Lane:** None. **D. Bissen:** None. **W. Wen:** None. **N.F. Wong:** None. **K. Bhut:** None. **R. Shanley:** None. **G. Turrigiano:** None.

Poster

PSTR363: Visual System: Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.06/CC22

Topic: E.06. Vision

Title: Disentangling neural plasticity in visual cortex across task, stimulus and contexts

Authors: *R. SUN[1], M. MICHAELOS[2], C. STRINGER[2], M. PACHITARIU[2];
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Abstract: Widespread plasticity occurs in the firing rates of mouse visual cortical neurons as a consequence of context learning, task learning, and stimulus learning (Zhong et al, 2025). It is not well understood which kinds of learning correspond to which neuronal changes, what plasticity persists outside of the task, or how different visual cortical areas may have similar or different plasticity rules. To disentangle these different factors, we established a novel sensory discrimination paradigm, where two unrelated visual textures were associated with reward, while another two unrelated textures were not. A set of mice quickly learned to discriminate between the rewarded and unrewarded textures (task cohort), while a second set of mice underwent the same visual experience without task training (unsupervised cohort). We recorded neural activity chronically throughout learning, and in additional non-training sessions before and after task sessions. By comparing neural discrimination within the rewarded and within the unrewarded category as well as between the rewarded and unrewarded categories, we could dissociate changes in stimulus selectivity from changes in reward category selectivity. We found that increases in neurons selective to reward/non-reward categories were concentrated in higher-order visual areas and absent in the primary visual cortex. Changes in stimulus-selectivity were observed in both primary and higher-order visual cortex, and were more prominent in the unsupervised cohort compared to the task cohort. Both of these types of changes (stimulus and category) were confined to the task context, while outside the task context we found a subpopulation of V1 neurons that responded to all trained stimuli substantially more than to novel stimuli, suggesting these neurons encode stimulus familiarity. Such signals were absent in higher-order visual areas. Our results pave the way towards a more granular understanding of neural plasticity in sensory cortical areas.

Disclosures: R. Sun: None. **M. Michaelos:** None. **C. Stringer:** None. **M. Pachitariu:** None.

Poster

PSTR363: Visual System: Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR363.07/CC23

Topic: E.06. Vision

Support: R01-MH122478 (to AAB, AH, and MS)
K99-EY033976 (to BR)

Title: MGE-Derived Interneurons Establish a Molecular Prodrome and Remain Required for Induced Plasticity

Authors: P. MARCHETTA[1], N. SANTIAGO[4], B. RAKELA[7], D. M. STEFFEN[8], T. SUZUKI[2], J. BIGELOW[3], A. ALVAREZ-BUYLLA[5], M. P. STRYKER[6], *A. R. HASENSTAUB[3]; [2]Otolaryngology, [3]Otolaryngology - Head and Neck Surgery, [1]UCSF, San Francisco, CA; [5]Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res., [6]Ctr. for Integrative Neurosci, Dept Physiol, [4]Univ. of California San Francisco, San Francisco, CA; [7]Neurosci., Sci. Corp., San Francisco, CA; [8]Brain Hlth., Abbott Labs., Columbus, OH

Abstract: Transplantation of embryonic cortical interneuron (cIN) precursors from the medial ganglionic eminence (MGE) into the postnatal visual cortex reopens ocular-dominance plasticity in the mature mouse brain. This transplant-induced critical period (CP) emerges ~35 days after transplantation, matching the age at which endogenous parvalbumin- and somatostatin-expressing cINs support the juvenile CP, despite the older host environment. How and when exactly transplanted cINs re-engage plasticity, and whether the same molecular programs underlie endogenous and induced CPs, remains unclear.

We addressed this with two complementary approaches. First, we profiled the visual cortex by single-cell RNA sequencing across endogenous and transplant-induced CPs, using Nkx2.1;Ai14 MGE donors to label transplanted cINs. Tissue was collected before monocular deprivation (MD), at peak plasticity one day after MD, and after CP closure following five days of MD. Endogenous CP animals, MGE-transplanted adults, and sham controls were pooled in biological replicates. This design allowed us to compare transcriptional dynamics across cortical cell types and plasticity states. CP-associated gene-expression changes were not uniform across cortex, but showed differentially expressed genes in specific glutamatergic populations. Unexpectedly, several signatures that were observed at peak plasticity were already present before MD in transplanted animals, suggesting that the induced CP is preceded by a molecular prodrome that prepares the circuit for experience-dependent change.

Second, we tested whether transplanted cIN activity is required during the induced CP. MGE precursors from Nkx2.1;Ai167 donors were transplanted into the visual cortex, enabling red-light manipulation of ChrimsonR-expressing transplant cINs. During five days of MD, mice were housed in darkness except for four hours of visual stimulation per day, paired with randomized optogenetic or sham stimulation designed to disrupt meaningful transplant cIN activity. Ocular dominance was then measured with Neuropixels recordings in binocular V1. Sham-stimulated transplanted mice showed a strong ocular-dominance shift, whereas optogenetically stimulated mice showed markedly reduced plasticity.

Together, these results suggest that transplanted interneurons establish a preparatory transcriptional state and remain functionally required during the induced CP. This work also identifies candidate cell-type-specific molecular programs that may allow plasticity to be re-engaged in the mature cortex, with implications for neural repair and rehabilitation.

Disclosures: P. Marchetta: None. **N. Santiago:** None. **B. Rakela:** None. **D.M. Steffen:** None. **T. Suzuki:** None. **J. Bigelow:** None. **A. Alvarez-Buylla:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arturo Alvarez-Buylla is cofounder, serves on the scientific advisory board, and owns shares in Neurona Therapeutics.. **M.P. Stryker:** None. **A.R. Hasenstaub:** None.

Poster

PSTR363: Visual System: Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR363.08/CC24

Topic: E.06. Vision

Support: NIH R01EY037733
NSF GRFP
Thw Swiss National Science Foundation
Severin Hacker Fund for Vision Research
The Professor Amar G. Bose Research Grant Program

Title: Tuning metaplasticity in the adult visual cortex using flickering light

Authors: *F. REILLY-ANDUJAR[1], E. Y. WANG[2], T. DR CRAMER[3], S. ZHAI[1], N.-W. CHANG[4], Y.-W. CHANG[4], A. J. HEYNEN[1], M. F. BEAR[1];
[1]Picower Inst. for Learning and Memory, [2]Brain and Cognitive Sci., MIT, Cambridge, MA; [3]Picower Inst. for Learning and Memory, MIT, Cambridge, MA, MA; [4]Dept. of Med. Res., Natl. Taiwan Univ. Hosp., Taipei, Taiwan

Abstract: Synaptic connections in the brain are refined by sensory experience during an early postnatal critical period, but by adulthood synaptic connectivity is resistant to further changes. A consequence of lost plasticity is limited recovery from brain injury, disease, or adverse sensory experience that occurs early in life. There is great interest in treatments that can promote synaptic modifications in the adult brain. In a wide variety of contexts, it has been established that the qualities of synaptic plasticity are not fixed but rather vary on the recent history of cellular or synaptic activity. This plasticity of plasticity, or metaplasticity, explains why temporary manipulations of brain activity (e.g. drugs, transcranial stimulation, or sensory deprivation) can set the stage for subsequent, potentially therapeutic, long-lasting synaptic modifications. Here we tested the hypothesis that plasticity in the adult mouse primary visual cortex is influenced by prior exposure to temporally modulated light and discovered that different flicker frequencies have qualitatively different effects. Exposure to 60 Hz light-flicker increased microglia density,

depleted perineuronal nets (PNNs), and restored ocular dominance plasticity in response to brief monocular deprivation (MD). Exposure to 40 Hz light-flicker enabled ocular dominance plasticity, but it did so in a distinct way without PNN remodeling. A key distinction is that unlike 60 Hz flicker, which enabled depression of synaptic strength by MD, 40 Hz flicker promoted synaptic strengthening. Indeed, we found that 40 Hz flicker primed a rapid and robust recovery from the effects of long-term MD that failed to occur after 60 Hz flicker. Thus metaplasticity can be non-invasively "tuned" by light flickering at different frequencies to encourage different forms of synaptic plasticity in the cerebral cortex, including modifications that enable recovery of function.

Disclosures: F. Reilly-Andujar: None. **E.Y. Wang:** None. **T. Dr Cramer:** None. **S. Zhai:** None. **N. Chang:** None. **Y. Chang:** None. **A.J. Heynen:** None. **M.F. Bear:** None.

Poster

PSTR363: Visual System: Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.09/CC25

Topic: E.06. Vision

Support: NIH Grant R01EY034092

Title: Abnormal visual experience impairs alignment-tolerant depth perception by disrupting the development of relative disparity coding in visual cortex

Authors: C. BARR[1], ***J. M. SAMONDS**[2];
[1]Univ. of Texas at Austin, Austin, TX; [2]Univ. of Texas At Austin, Austin, TX

Abstract: We recently showed that 30 days of monocular deprivation during the critical period of binocular visual cortex development impairs binocular depth perception and disrupts the cortical organization of disparity tuning in mice. One consequence of this disruption is reduced trial-to-trial reliability of disparity-dependent neural responses. A potential source of this variability is fluctuations in binocular alignment, which alter the disparities projected onto the retinas. Neurons that encode relative disparity by comparing disparities across regions of visual space are predicted to be tolerant to such fluctuations, whereas neurons encoding absolute disparity are not. To test this hypothesis, we first measured behavioral disparity discrimination and found that mice exhibited significantly lower discrimination thresholds when a reference disparity surround was present. We then used two-photon calcium imaging to measure disparity tuning in visual cortical neurons while varying the disparity of a central vertical strip under three surround conditions (zero, near, and far disparity). Neurons encoding relative disparity were expected to shift their tuning curves by an amount corresponding to the surround disparity, whereas neurons encoding absolute disparity were expected to maintain stable tuning regardless of surround disparity. Analysis of tuning-curve shifts revealed evidence for neurons consistent with relative- and absolute-disparity representations. Notably, the population of relative

disparity-tuned neurons was markedly reduced following 30 days of monocular deprivation. These findings suggest that relative disparity coding supports alignment-tolerant depth perception by reducing variability arising from changes in binocular alignment and that normal visual experience during the critical period is required for the development of this robust neural representation.

Disclosures: C. Barr: None. **J.M. Samonds:** None.

Poster

PSTR363: Visual System: Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.10/CC26

Topic: E.06. Vision

Title: Evidence that PNU-282987 stimulated adult primary retinal pigment epithelium induces neurogenesis in adult primary pig retinal cell culture: Co-localization of Ki67 and beta III tubulin.

Authors: *D. M. LINN[1], S. WARNER[1], C. L. LINN[2];
[1]Biomed. Sci., Grand Valley State Univ., Allendale, MI; [2]Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: Evidence exists showing that activation of α7 nAChRs in adult rodents can lead to the generation of new retinal neurons. It is hypothesized that activation of α7 nAChRs on retinal pigment epithelium (RPE) with the selective α7 nAChR agonist, PNU-282987, induces the release of signaling molecules that cause retinal Müller glia to re-enter the cell cycle and produce neuronal progenitor cells. Previously, we reported on the development of a 2-step culture system that could provide a more 'high throughput' approach to these earlier *in vivo* rodent studies. This approach reduces the assay time (20 days to 7) and eliminates the need for animal care. The protocol starts with the isolation of RPE from adult pig eyes that are cultured for 2 days with, or without, α7 agonist. After 2 days in culture, RPE are rinsed and transferred to a separate culture of freshly dissociated adult pig retinal cells. RPE are incubated with retinal cells for 5 days, then cell numbers are quantified. When retinal cells were co-cultured with unexposed primary RPE, we observed a 34.9% increase ($p < 0.05$, N=8) in cell numbers vs control retinal culture. When retinal cultures were co-cultured with primary RPE exposed to PNU-282987, a maximal effect was observed with 200 nM. The maximal increase in cell numbers was 162.5% ($p < 0.01$, N=8). There was a decline in the increase with 500 nM compared to 200 nM. The increase in cell numbers was blocked when the selective α7 antagonists, α-BTX (100 nM) and MLA (100 nM), were applied to RPE after isolation and before PNU-282987 treatment. To investigate that the observed increase in cell numbers is due to dividing cells, IHC studies using Ki67 were conducted. Ki67 labeling showed a dose dependent relationship with exposure to the α7 agonist. An average of 27.7% of cells were labeled with Ki67 in control retinal cultures which increased significantly to 89.4% in the presence of 200 nM PNU-282987 ($p < 0.01$, N = 3). Most recently,

to explore if the dividing cells were presumptive neuronal progenitors, we co-labeled cells with Ki67 and beta III tubulin. We observed 1.2% co-labeling in control retinal cultures, 6.9% with un-stimulated RPE, 16.4% with RPE + 100 nM agonist, and 24.5% with RPE + 200 nM agonist ($p < 0.01$ for control vs. 200 nM, $N = 3$). Here we expand on previous reports that exposed and unexposed primary RPE can induce cell division in primary retinal cell culture numbers in an adult large mammal system after exposure to PNU-282987. Our results indicate that dividing cells are presumptive neuronal progenitor cells. Further experiments need to be conducted to expand on the mechanisms involved with the effect on retinal cells following stimulation of RPE by PNU-282987.

Disclosures: D.M. Linn: None. **S. Warner:** None. **C.L. Linn:** None.

Poster

PSTR363: Visual System: Plasticity

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.11/CC27

Topic: E.06. Vision

Support: NIH R15 #EY027970

Title: Activation of alpha7 nicotinic receptors on adult mammalian retinal pigment epithelium via PNU-282987 treatment drives transcriptional activation of key genes involved in non-mammalian vertebrate retinal regeneration

Authors: *G. NOLASCO DE CARVALHO, H. VANZO-SPARKS, C. L. LINN;
Western Michigan Univ., Kalamazoo, MI

Abstract: Activation of the α7 nicotinic acetylcholine receptor (α7 nAChR) has emerged as a promising strategy to stimulate retinal neurogenesis in adult mammals. Prior work from this laboratory demonstrates that the α7 nAChR agonist PNU-282987 induces the formation of Müller glia-derived progenitor cells (MDPCs), leading to the generation of new neurons in adult mice. Further studies found that PNU-282987 treatment triggers mitotic activity across all layers of the neural retina. We hypothesize that PNU-282987 acts on a7 nAChRs on the RPE to induce retinal neurogenesis via conserved developmental and non-mammalian vertebrate regeneration pathways, working to overcome intrinsic mammalian limitations preventing recovery from vision loss as a result of disease, injury, or aging. To investigate, primary RPE cells were isolated from adult (3-6 month old) 129 SvJ mice and cultured in 100mm plates. Cells were treated with media containing 100 nM PNU-282987 with 1% DMSO (experimental) or 1% DMSO alone (vehicle control) across early and late timepoints. Total RNA was isolated using the Direct-zol RNA Miniprep kit, assessed for quality, and submitted for bulk RNA sequencing. Based on the number of significantly differentially expressed genes (sDEGs), analyses prioritized the 15 minute, 1 hour, and 8 hour timepoints (sDEG counts, respectively: 3662, 3995, 2920). Raw reads were processed with *fastp* for quality control, aligned to the *Mus musculus* (GRCm39) reference

genome, and calculated as FPKM for point-to-point comparisons against DMSO controls. Transcriptomic profiling revealed differential expression of key genes in the Sonic Hedgehog (Shh), Bone Morphogenetic Protein (BMP), and Wnt pathways. Large fold changes for targets like *Sostdc1* (Wnt/BMP antagonist) and *Gli2* (Shh activator) switched between upregulation and downregulation across timepoints. Specifically, *Gli2* exhibited early activation (2-5 fold upregulation at 15 min-1 hr) and late suppression (4 fold downregulation at 8 hr), while *Sostdc1* showed a biphasic pattern (9 fold upregulation at 15 min, 3 fold downregulation at 1 hr, 8 fold upregulation at 8 hr). Furthermore, primary adult mammalian Müller glia transcriptomes after co-culture with treated primary RPE showed Shh upregulation at 2 hours. KEGG analysis indicated downstream PNU-282987-mediated signaling cascades converge on G-protein coupled receptor activation pathways within the RPE. Ongoing validation includes RT-qPCR, ELISA, IHC and sequencing in triplicate. Investigating the role of PNU-282987 treatment in the retina can potentially lead to new treatments for those affected by visual deficits that result from neurodegeneration.

Disclosures: G. Nolasco de Carvalho: None. **H. Vanzo-Sparks:** None. **C.L. Linn:** None.

Poster

PSTR363: Visual System: Plasticity

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Program #/Poster #: PSTR363.12/CC28

Topic: E.06. Vision

Support: NEI EY027970

Title: Signaling mechanisms that promote Müller glia reprogramming following PNU-282987 treatment in mammalian cell culture

Authors: *H. VANZO-SPARKS[1], D. M. LINN, Jr.[3], C. L. LINN[2];
[2]Biol. Sci., [1]Western Michigan Univ., Kalamazoo, MI; [3]Biomed. Sci., Grand Valley State Univ., Allendale, MI

Abstract: Previous studies from this laboratory have demonstrated that the application of the selective alpha-7 nicotinic acetylcholine receptor (nAChR) agonist, PNU-282987, can induce retinal neurogenesis in injured and uninjured adult murine models. These findings suggest that PNU-282987 acts on alpha-7 nAChRs located in the retinal pigment epithelium (RPE), triggering the release of a signaling molecule to influence the apical processes of Müller glia (MG) cells. It is hypothesized that this signaling molecule stimulates MG proliferation and formation of retinal progenitor cells. While substantial work has been done to elucidate the response of RPE cells to PNU-282987, the mechanisms underlying MG transformation in response to this agonist remain unexplored. Previous RNA-seq studies investigating the transcriptomic response of MG cells to PNU-282987 revealed the upregulation of pathways and genes associated with retinal regeneration and development. Based on these findings, we

hypothesize that PNU-282987 promotes neurogenesis in adult MG by activating a network of developmental signaling pathways and transcriptional regulators, collectively driving the transition from a gliotic response to a progenitor-like state. In this study, we verify that cultured MG cells proliferate and form progenitor cells in the presence of PNU-282987, and we further elucidate the mechanisms through which it induces neurogenesis. To assess cell cycle incorporation and progenitor formation, primary MG and RPE cultures were isolated from 3-month-old 129/SvJ mice and grown to confluency. To evaluate which of the highly enriched pathways identified by RNA-seq contribute to PNU-282987's neurogenic effect in MG, cultures were grown to confluency and co-cultured with RPE treated with 100 nM PNU-282987 and 1% DMSO in experimental groups or with 1% DMSO in control groups. RNA-seq revealed sonic hedgehog pathway (Shh) activation, suggesting a potential role in PNU-282987-mediated MDPC formation. To further investigate this pathway's effect, sonic hedgehog signaling was inhibited when Cyclopamine (10 μg/mL) was added to the culture medium. The resulting cultures were subjected to RNA extraction for RT-qPCR analysis to assess cell cycle incorporation. When applied to MG, Cyclopamine downregulated Gli1, Ptch1, and Hhip, Shh target genes, by 1-3 fold changes (n=3) compared to PNU-282987-treated MG, whereas Cyclopamine added to RPE did not result in downregulation (no fold change). The results from these experiments reveal that Shh activation may be occurring after PNU-282987 treatment, where RPE releases a Shh ligand that binds to Shh receptors on MG cells.

Disclosures: H. Vanzo-Sparks: None. **D.M. Linn:** None. **C.L. Linn:** None.

Poster

PSTR363: Visual System: Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.13/CC29

Topic: E.06. Vision

Support: VR220084

Title: Targeting alpha7 nicotinic receptors to restore retinal structure and function after blast injury in adult mammals

Authors: *J. B. SPITSBERGEN, C. L. LINN;
Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: Vision loss is often a serious consequence of blast-related ocular injuries, which accounts for almost 13% of all battlefield injuries. Recent studies have shown that eyedrop application of a specific alpha-7 nicotinic acetylcholine receptor agonist, PNU-282987, has potential to induce neurogenesis in damaged adult mammalian retinas. The objective of this research is to evaluate the structural and electrophysiological integrity of the mammalian visual pathway following ocular blast trauma and eyedrop treatment with PNU-282987. The hypothesis to be tested in this study is that application of PNU-282987 immediately following ocular blast

trauma causes cellular and functional changes in the mammalian visual system, including the retina, optic nerve and optic tract within the brain. Modeling primary ocular blast trauma involved using a modified paintball gun to deliver a single blast of 35 PSI focused onto one eye of adult transgenic mice expressing TdTomato Müller glia (3-6 months old; both sexes). 4 weeks of eyedrop treatment with PNU-282987 has been shown to alleviate the loss of cells in all retinal layers observed following exposure to a blast of 35 PSI. Neurogenesis and functional recovery, after 4 weeks of PNU-282987 treatment, were evaluated through immunohistochemical analysis and electroretinogram (ERG) recordings. Following eyedrop treatment with PNU-282987, 15.26% +/- 4.3 of photoreceptors and 8.75% +/- 1.2 were observed to double label with TdTomato, indicating newly formed Müller glia-derived neurons (*n=6, p<.05)*. TdTomato positive retinal ganglion cell axons were observed in the optic tract when cholera toxin B and GAP43 were used to trace/co-label newly formed axons extending from the retina into the brain. In addition to the immunohistochemical results indicating growth of new neurons in the retina and visual pathway, the electrophysiological results indicate significant recovery of function that was lost following induction of blast injury. ERG waveforms evaluated included: a wave, b wave, oscillatory potentials, photopic negative response, pattern ERG, and visually evoked potentials. All elements of the ERG recordings displayed a significant and lasting loss of amplitude following ocular blast trauma (30-57%) compared to a significant recovery of amplitude after 4 weeks of eyedrop treatment with PNU-282987 (35-190%) (*n=6, p<.05*). These are the first experiments designed to address both morphological and electrophysiological changes in the mammalian visual pathway following blast exposure and eyedrop treatment with PNU-282987. This research can lead to treatment strategies that address neurodegeneration.

Disclosures: J.B. Spitsbergen: None. **C.L. Linn:** None.

Poster

PSTR363: Visual System: Plasticity

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Program #/Poster #: PSTR363.14/CC30

Topic: E.06. Vision

Support: NIH Grant EY035138

Title: Cell type-specific aggrecan deletion and ocular dominance plasticity

Authors: *T. BROWN, X. MA, A. W. MCGEE;
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Abstract: Perineuronal nets (PNNs) have been proposed to restrict experience-dependent plasticity during developmental critical periods. To test the role of PNNs in critical period closure, we selectively eliminated aggrecan (Acan), an essential PNN component, from distinct neuronal populations in mouse visual cortex using conditional Cre-lox strategies. We then assessed ocular dominance plasticity and differential gene expression using in vivo two-photon

calcium imaging and Xenium 5K spatial transcriptomics.Because PNNs primarily surround parvalbumin-positive (PV+) interneurons, we first deleted Acan using inhibitory neuron-specific Cre drivers. Surprisingly, selective loss of Acan from inhibitory neuron-associated PNNs did not alter critical period closure or gene expression patterns. These findings were consistent across multiple inhibitory neuron Cre lines.Next, we deleted Acan pan-neuronally across all cortical neuronal cell types with BAF53b-Cre. In contrast to inhibitory neuron-specific deletion, pan-neuronal Acan deletion extended the critical period, permitting ocular dominance plasticity after normal visual system maturation. Pan-neuronal deletion also increased expression of several immediate early genes associated with experience-dependent plasticity.Together, these findings demonstrate that elimination of PNNs surrounding inhibitory neurons alone is insufficient to close the critical period and suggest that broader neuronal Acan expression contributes to limiting cortical plasticity in the mature visual cortex.

Disclosures: T. Brown: None. **X. Ma:** None. **A.W. McGee:** None.

Poster

PSTR363: Visual System: Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.15/DD1

Topic: E.06. Vision

Support: NIH Grant R01 EY035138

Title: Perineuronal nets do not close the critical period for visual plasticity

Authors: *H. MA[1], E. CROUSE[3], X. MA[1], S. QIU[4], A. W. MCGEE[2];
[2]Dept. of Translational Neurosci., [1]Univ. of Arizona, Phoenix, AZ; [3]Univ. of Louisville, Louisville, KY; [4]Basic Med. Sci., Univ. of Arizona COM-PHX, Phoenix, AZ

Abstract: Perineuronal nets (PNNs) are proposed to close the critical period for plasticity in the developing visual system. Aggrecan is an essential component of PNNs. Here we investigated whether PNNs are required to close the critical period by deleting expression of aggrecan from different populations of neurons and testing whether adult mice (P60+) retained ocular dominance (OD) plasticity that is otherwise restricted to the critical period (postnatal day 19-32). We deleted the gene encoding aggrecan, *Acan*, from inhibitory neurons by combining a 'floxed' conditional allele of *Acan* with several different Cre driver lines with overlapping expression patterns: *Parvalbumin (PV)-Cre*, *DLX5/6-Cre*, and *GAD2-Cre*. In addition, we employed a Cre driver for excitatory cortical neurons, *Camk2a-Cre*, and a pan-neuronal Cre driver, *BAF53b-Cre*. Deleting *Acan* expression from PV interneurons with any one of these distinct Cre drivers for inhibitory neurons eliminated PNNs but not affect the closure of the critical period as the ocular dominance (OD) of adult mice was insensitive to brief (4-5 days) monocular deprivation (MD) as measured with multi-unit electrophysiologic recordings. By comparison, deletion of *Acan* with *BAF53b-Cre* or *Camk2a-Cre* prevented the critical period from closing and adult mice

displayed OD plasticity in response to 4-5 days of MD. This sustained critical-period plasticity in adult mice was accompanied by a reduction in the cortical excitatory synaptic drive onto PV interneurons in layer 2/3 of visual cortex. In contrast to predominant models, we propose that the OD plasticity reported for adult rodents following treatment with the enzyme chondroitinase ABC has misattributed to PNN digestion, when the true mechanism is loss of neuropil aggrecan.

Disclosures: H. Ma: None. **E. Crouse:** None. **X. Ma:** None. **S. Qiu:** None. **A.W. McGee:** None.

Poster

PSTR363: Visual System: Plasticity

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.16/DD2

Topic: E.06. Vision

Support: NIH R01EY020517

Title: Temporal-order judgment in late-sighted children: preserved plasticity late into childhood

Authors: *M. VOGELSANG[1], L. VOGELSANG[1], P. GUPTA[2], N. LALL[3], M. JAIN[4], C. RALEKAR[5], S. NARANG[3], P. SETHI[3], S. GANESH[6], P. SINHA[1];
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Abstract: Determining which aspects of visual development depend on early experience, and which are resilient to its deprivation, is central to understanding critical periods in neural development. While early visual deprivation is known to lastingly impair certain perceptual capacities, we here examined its consequences for temporal-order judgment — a function that, depending on spatially resolved input, might be expected to share this vulnerability. This capacity may constitute a key developmental building block for transforming an infant's 'blooming buzzing confusion' into an organized sensorium. However, several factors underlying its genesis remain unclear. In particular, is early experience with spatially distinct visual entities necessary to learn their temporal arrangement, given that temporal relationships between different entities may be meaningful only if they are spatially resolvable? To address this question, we studied a unique group of individuals with prolonged visual deprivation due to dense congenital cataracts who received sight surgeries late in childhood. We longitudinally tracked 13 patients from immediately before surgery through the first post-operative month and also examined 15 late-sighted individuals several years after surgery. Our control group comprised 37 normally-sighted individuals. In each trial, participants observed two transiently flashed visual stimuli with temporal lags between 17 and 500 ms and indicated which stimulus appeared first. Notably, we found that patients with several years of post-operative visual

experience performed fully on par with controls. However, this ability was not evident immediately after surgery but followed a protracted progression, mirroring normal development. We next examined whether such gradual progression may confer any adaptive benefits to the visual system. Our computational simulations with video-based neural networks revealed that incorporating temporal degradations into early training phases yielded more temporally-extended model representations and improved generalization, thereby conferring important advantages for robust visual development. Taken together, these findings reveal remarkable neural plasticity late into childhood for acquiring temporal-order judgments, in contrast to several other visual functions, such as holistic perceptual organization. They further suggest that time-based binding mechanisms may facilitate visual learning in the late-sighted, and that gradual temporal maturation may confer adaptive advantages, with implications for typical, atypical, and computational visual development.

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Poster

PSTR363: Visual System: Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.17/DD3

Topic: E.06. Vision

Support: NIH R01EY020517

Title: Compromised holistic perceptual organization in late-sighted children: potential role of initially degraded visual input

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Abstract: A longstanding question in the neural development of visual systems is whether early experience is necessary for the emergence of holistic perceptual organization, and whether visual deprivation beyond putative critical periods irreversibly prevents this. Here, we had a unique opportunity to address this question by examining the consequences of curtailing early visual experience on Gestalt-like perceptual grouping mechanisms later in life. Specifically, we studied a rare population of visual observers - children from rural India who were born blind and gained sight through surgical intervention late in childhood. We adapted a paradigm previously used with normally-sighted infants. Participants viewed square arrays of elements arranged in a uniform grid, where grouping was induced through similarity in luminance or figural form along

alternating rows or columns, and reported whether they perceived vertical or horizontal organization. Longitudinal assessments of 16 patients from pre-operative to many months post-operative status revealed persistently poor performance. Despite notable gains in other visual abilities, such as temporal order judgments, participants exhibited no improvement over time and remained substantially below matched controls. This deficit was consistent across all grouping cues. Complementary computational simulations suggest a candidate mechanistic account for these findings: the deficits may arise from commencing visual experience with higher-fidelity input than is available to neonates. Models exposed to developmentally inspired degraded-to-undegraded input trajectories formed representations that more strongly encoded holistic organization in Gestalt stimuli. In contrast, models trained without this developmental progression, akin to the experience of the late-sighted, failed to develop such organization. Together, these results provide evidence that early-onset blindness yields lasting impairments in Gestalt-like grouping, and point to an account that complements critical-period based ones. While the latter attribute the deficit to input arriving after the relevant developmental window has closed, we suggest that not only the timing but also the degraded quality of early visual experience may be key for the emergence of holistic organization. Besides revealing the consequences of early deprivation on the important perceptual dimension of Gestalt organization, these findings also help advance our understanding of dependencies within typical developmental choreography, and highlight the usefulness of more developmentally-aligned training regimens for computational models.

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Poster

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Program #/Poster #: PSTR363.18/DD4

Topic: E.06. Vision

Support: Support from Freedom Together Foundation
DoE Grant DE-SC0022997
NIH Grant R01EY023037
Support from Martynov Family Fund

Title: Ultra-fast novelty detection in mouse V1: A memory trace in early visual cortex

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Abstract: The primary visual cortex (V1) performs complex computational roles ranging from fast feedforward feature extraction to slower predictive signaling mediated by feedback from

higher visual areas. Here we reveal a new computational role for V1 by showing that it harbors an ultra-fast novelty detection mechanism that operates concurrently with feedforward sensory processing. Using high-density linear probe recordings in mouse V1, we measured responses to familiar versus novel phase-reversing gratings. Surprisingly, differential responses emerged as early as 75 ms after stimulus onset. Using decoders trained on both instantaneous and longer-timescale multiunit activity, we found that information required for discriminating between familiar and novel stimuli is available across the entire cortical depth from 75-100 ms post-onset, with persistent decoding possible in L2/3 over hundreds of milliseconds. This rapid divergence was laminar-specific: earliest differences appeared in lower L2/3 and L4, followed by L5 and L6. The presence of novelty signals in L4, the primary thalamorecipient layer, suggests that this computation does not require feedback from higher areas. Instead, novelty detection is embedded locally within early V1 circuits, which actively construct a familiarity prediction within milliseconds of stimulus onset, a latency previously attributed only to feedforward feature detection. This reveals that early sensory areas can perform active, memory-guided computation on ultra-fast timescales.

Disclosures: T. Chauhan: None. **D. Montgomery:** None. **M.F. Bear:** None.

Poster

PSTR363: Visual System: Plasticity

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Program #/Poster #: PSTR363.19/DD5

Topic: E.06. Vision

Support: NIH Grant EY030164
Massachusetts Lions Eye Research Fund
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Title: Paired pulse responses reflect critical period status in mouse V1

Authors: *E. D. GAIER[1], D. A. BOWEN[2], R. TIWARI[2], D. P. MONTGOMERY[3], S. ZHAI[4], J. P. GAVORNIK[2], M. F. BEAR[4];
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Abstract: Experience-dependent plasticity in primary visual cortex (V1) declines with maturation and critical period closure, in part because of increasing intracortical inhibition. A major barrier to developing treatments for amblyopia is the lack of physiological biomarkers that report cortical plasticity state in vivo. We tested the hypothesis that relative responses to repeated visual stimulation provide a noninvasive measure of inhibitory tone and critical period status. Visually evoked potentials (VEPs) were recorded from binocular V1 of awake juvenile (P28-P36) and adult (P56+) mice. Responses were measured during trains of visual stimulation and paired-pulse paradigms using flash, sinusoidal grating, and checkerboard stimuli at interstimulus

intervals (ISIs) of 67, 133, 267, and 533 ms. Paired-pulse ratio (PPR) was calculated as the amplitude of the second response divided by the first. In a separate cohort, adult mice received monocular intravitreal tetrodotoxin (TTX), a manipulation known to promote recovery from amblyopia beyond the critical period. In addition, field recordings in layer 2/3 of acute slices examined paired-pulse responses across a similar range of ISIs. Juvenile mice exhibited enhanced responses to rapid (6-8 Hz) visual stimulation relative to low-frequency stimulation (2 Hz), whereas this enhancement was absent in adults (juvenile n=8-11; adult n=8). Paired-pulse experiments revealed significantly greater PPRs in juveniles than adults at short ISIs, particularly 67 ms, for both sinusoidal grating and checkerboard stimuli, whereas flash stimuli showed minimal age dependence (n=6). Age-related differences diminished at longer ISIs. Importantly, intravitreal TTX restored juvenile-like response ratios in adult animals (n=19). Consistent with the in vivo findings, layer 2/3 field recordings in acute V1 slices demonstrated higher PPRs in juvenile (n=4-8 slices from 3-5 mice) than adult cortex (n=7-8 slices from 3-5 mice) following stimulation of either layer 4 or white matter inputs. These findings identify paired-pulse suppression as a physiological signature of developmental changes in visual cortical circuitry and support the interpretation that short-interval PPR provides a physiological correlate of inhibitory tone associated with critical period closure. Restoration of juvenile-like response ratios following TTX demonstrates sensitivity to manipulations that reverse critical-period constraints on plasticity. Relative responses to repeated visual stimulation may therefore provide a scalable biomarker of cortical plasticity and treatment responsiveness in amblyopia.

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Poster

PSTR363: Visual System: Plasticity

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Support: National Key R&D Program of China 2025YFC3608500
National Natural Science Foundation of China Grant 81770956
Project of Tianjin 131 Innovative Talent Team Grant 201936

Title: Pharmacological inhibition of Sema3A restores ocular dominance plasticity in the adult visual cortex

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Abstract: The visual cortex undergoes a critical period during early development, during which neural circuits exhibit heightened sensitivity to visual experience. In the primary visual cortex

(V1), this plasticity gradually declines with the maturation of perineuronal nets (PNNs), which stabilize neural circuits and constrain ocular dominance plasticity (ODP). Reactivating plasticity in the adult V1 remains a major challenge. Here, we used adult C57BL/6 mice to test whether pharmacological inhibition of Sema3A, an endogenous regulator of synaptic plasticity and PNNs, can restore ODP. Monocular deprivation (MD) was performed for 4 days concurrently with local injection of the Sema3A inhibitor SM-345431 or vehicle control into V1. *In vivo* multichannel extracellular electrophysiology was performed to record the spiking activity in V1, and immunofluorescence staining was used to assess PNN structure. We found that MD alone induced no significant OD shift in control adult mice. However, injection of Sema3A inhibitor significantly reduced contralateral bias index from 0.682±0.018 (mean ± SEM, n=6 mice) to 0.613±0.019 (n=6 mice, P=0.0182, Mann-Whitney U) and also lowered ocular dominance index from 0.379±0.023 (n=205 cells) to 0.260±0.018 (n=299 cells, $P < 0.0001$). Under visual stimulation to the ipsilateral (non-deprived) eye, neurons in the drug group showed a marked increase in firing rate, while no change was observed under stimulation to the contralateral (deprived) eye. Furthermore, high-magnification confocal imaging revealed that the drug group had increased PNN hole density compared with control mice, indicating a looser PNN ultrastructure. These results suggest that inhibiting the binding of Sema3A to its receptor attenuates Sema3A-dependent repression of synaptic plasticity and concurrently remodels PNN ultrastructure toward a more porous state, thereby restoring ODP in the adult mouse V1. This study provides a novel molecular target that could be used in intervention strategies for treating adult amblyopia and other visual developmental disorders.

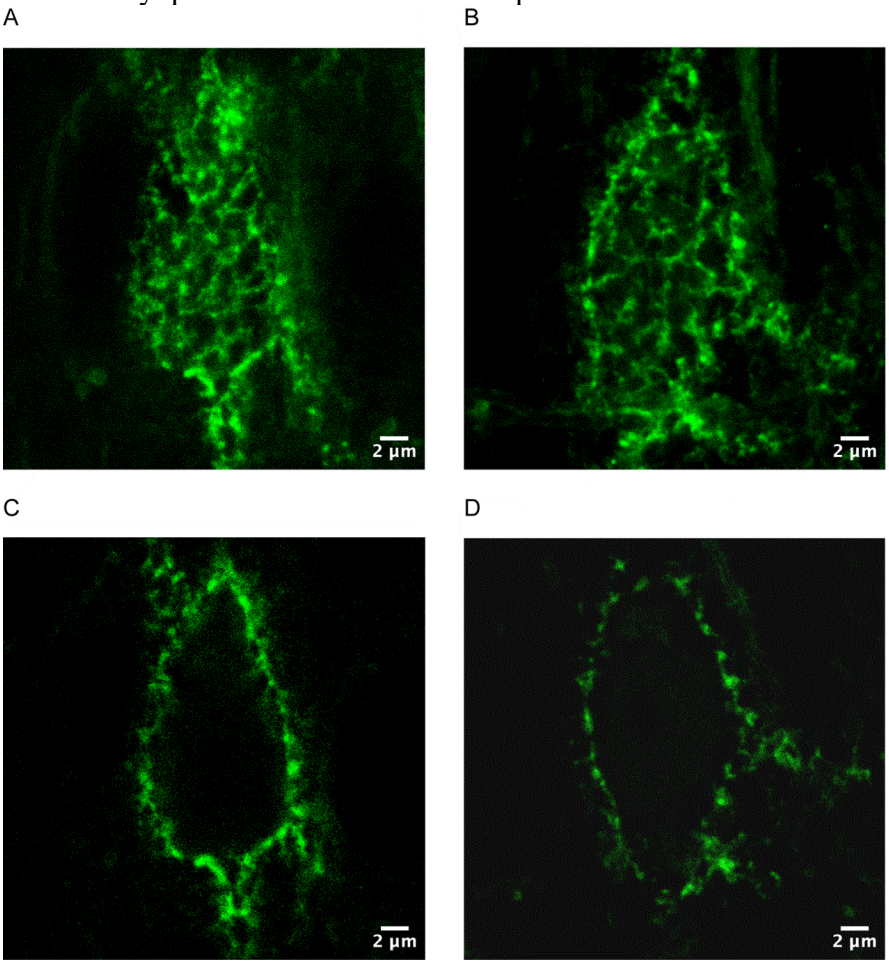


Figure 1. High-magnification imaging of PNN structure in V1 of MD mice following injection of Sema3A inhibitor versus vehicle control. (A) Drug-treated group showing a looser PNN structure, compared with the vehicle control group shown in (B). (C) Drug-treated group at the largest cross-sectional plane, exhibiting increased hole density, compared with the vehicle control group shown in (D). A,C from the same cell; B,D from the same cell. Scale bar: 2 μm.

Disclosures: X. Meng: None. **J. Liu:** None. **X. Shi:** None.

Poster

PSTR364: Eye Movements

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR364.01/DD7

Topic: F.01. Eye Movements

Support: JSPS KAKENHI Grant-in-Aid for Scientific Research (C) (Grant Number JP24K14586)
Nihon University research grant for 2025 Overseas Researchers

Title: Age- and Expertise-Dependent Predictive Saccade Strategies and Low-Beta Oscillatory Dynamics in Visuomotor Control

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Abstract: Anticipating the endpoint of a moving object is a fundamental visuomotor skill. An efficient mechanism is the predictive saccade, in which gaze disengages from smooth pursuit and shifts rapidly to the anticipated endpoint, freeing attentional resources while preserving temporal precision. Prior work implicates low-beta oscillations (13-15 Hz) in visuomotor regions-middle temporal cortex (MT) and frontal eye fields (FEF)-in predictive gaze control, yet how these mechanisms vary across the lifespan and with intensive visuomotor training remains unknown. We compared predictive saccade behavior and EEG-derived low-beta dynamics across four groups: adolescents (10-15 year), young adults (-20 year), older adults (40- year), and top-level eSports competitors. Participants performed a parabolic interception task (4.6 s total; target occluded after 2.3 s) requiring gaze to shift to the predicted endpoint and a button press at expected arrival. Eye movements were recorded with Gazefinder (50 Hz); EEG was sampled at 1000 Hz and low-beta amplitude extracted via the Hilbert transform. Eye-tracking revealed that young adults initiated predictive saccades earlier and with smaller endpoint and temporal errors than adolescents and older adults. eSports experts outperformed all groups, showing the earliest saccade initiation, smallest endpoint error, and most precise temporal judgments. Older adults exhibited the largest errors and latest initiation, whereas adolescents showed intermediate

performance consistent with ongoing developmental refinement. EEG analyses focused on MT- and FEF-adjacent electrodes. eSports players exhibited strong, sustained low-beta modulation beginning shortly after target onset. Young adults showed moderate enhancement, while adolescents and older adults displayed markedly attenuated oscillatory activity. Group differences in low-beta amplitude significantly predicted endpoint accuracy across participants. These findings demonstrate that predictive visuomotor control peaks in young adulthood and declines with age, but can be substantially enhanced through intensive training. The coupling between low-beta oscillations in MT and FEF and predictive saccade accuracy supports a predictive coding framework in which these rhythms coordinate anticipatory gaze behavior. Results have implications for sports science, cognitive aging, and sensorimotor rehabilitation.

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Poster

PSTR364: Eye Movements

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Program #/Poster #: PSTR364.02/DD8

Topic: F.01. Eye Movements

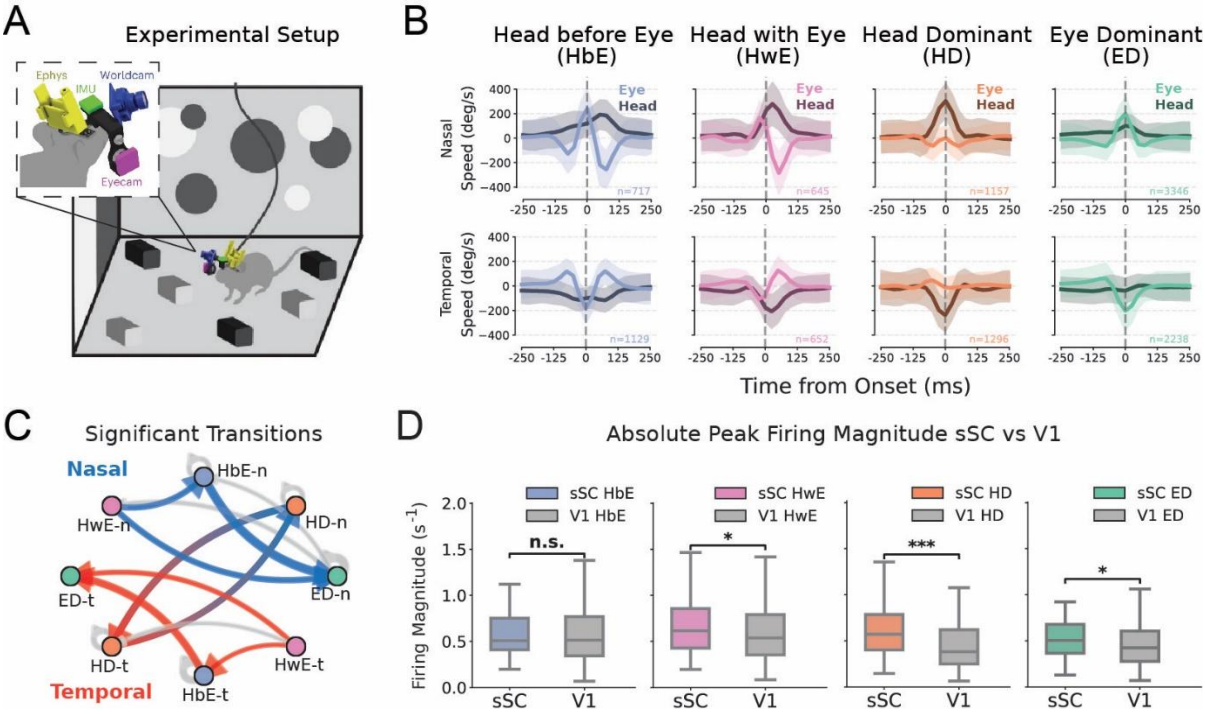
Support: NIH R01-NS121919

Title: Gaze shifts in freely moving mice comprise distinct head-eye coordination motifs

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Abstract: In freely moving mice, gaze shifts are conventionally defined as the head and eye coupled movements to redirect visual scenes and are treated as a single category, despite the diversity in how the head and eyes are coordinated to produce them. It remains unknown whether this category instead contains distinct and actively coordinated modes.
We combined high-resolution head and eye tracking with electrophysiology in primary visual cortex (V1) or superficial superior colliculus (sSC) in freely moving mice (C57BL/6J mice, 3-10 months, 4 mice per region; sSC 68 neurons, V1 279 neurons; Fig. 1A). Using peri-onset head-eye kinematics (±100 ms; velocity and acceleration), unsupervised data partitioning revealed four gaze shift motifs (Fig. 1B): Head-before-Eye (HbE, 16.51%), Head-with-Eye (HwE, 11.60%), Head-Dominant (HD, 21.94%), and Eye-Dominant (ED, 49.94%).
These motifs were stable and recovered across directions. They differed in locomotor state, with HwE showing the highest and HD the lowest post-onset body speeds ($p < 0.001$). The sequential organization of motifs was non-random: HD formed a recurrent direction-switching mode, whereas HwE-HbE-ED formed a directed transition chain (Fig. 1C). sSC neural peak firing

magnitudes exceeded V1 for HD, ED, and HwE, but not HbE (Fig. 1D).
These results indicate that gaze shifts in freely moving mice form a diverse and structured repertoire of head-eye coordination motifs.



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Poster

PSTR364: Eye Movements

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Program #/Poster #: PSTR364.03/DD9

Topic: F.01. Eye Movements

Title: visual pursuit and adaptive visual behavior in freely moving mice revealed by a head-mounted gaze-tracking system

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Abstract: Compared with frontal-eyed mammals, lateral-eyed rodents such as rats and mice have received relatively little direct investigation of gaze behavior during free movement, despite their widespread use in biological research. To address this gap, we developed a head-mounted

miniature gaze-tracking system to measure gaze position in freely moving mice. The device incorporates eye cameras and scene cameras, allowing simultaneous recording of pupil position and environmental images at 60 Hz. We further developed a behavioral calibration method to map mouse pupil position onto gaze location within the scene-camera field of view. We validated this behavioral calibration using calcium imaging of V1 neural representation in head-fixed, anesthetized adult mice. By comparing neural representation density with pupil gaze position, we found that the visual-field location corresponding to the pupil (defined as the optical center) did not overlap with the location of maximal neural representation density/minimal cortical magnification (defined as the neural center). These two points exhibited a consistent spatial offset across mice, with the neural center shifted toward the nasal side. We therefore established a gaze-tracking-based approach for localizing both the optical center and neural center in mice. Using this system, we observed robust active visual pursuit and other eye-movement behaviors during free exploration, foraging, and looming visual stimulation tasks. These gaze behaviors were context dependent, suggesting that mice dynamically coordinate pupil position, head movement, and environmental features to sample behaviorally relevant visual information. By comparing the statistics of estimated retinal image input during free movement with the spatial distribution of neural representation in V1, we further found that the distribution of sampled visual information was aligned with cortical representation density. Together, this work provides a new tool for investigating visual behavior in unrestrained lateral-eyed animals. Our findings suggest that mouse gaze behavior and V1 cortical organization are coordinated to support efficient visual sampling, reflecting an evolutionary adaptation for extracting behaviorally relevant information from natural environments.

Disclosures: Y. Zhou: None. **M. Wei:** None. **G. Shi:** None. **S. Xing:** None. **F. Liu:** None. **K. Liu:** None.

Poster

PSTR364: Eye Movements

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Program #/Poster #: PSTR364.04/DD10

Topic: F.01. Eye Movements

Support: R01NS129608
R01NS079518
NSF GRFP 241158

Title: Premotor neurons in the superior colliculus encode eye position and saccade kinematics

Authors: *A. BUTEAU, J. HUNT, N. FISHER, C. MINJAREZ, A. POLEG-POLSKY, G. FELSEN;
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Abstract: To efficiently and effectively navigate environments with rich visual stimuli, most species utilize a strategy known as active vision.This process involves the coordination of eye, head, and body movements to actively sample visual information so an organism can quickly obtain an understanding of their surroundings.Saccadic eye movements are a crucial component of active vision.These rapid, ballistic eye movements can serve to direct the eyes to a specific visual target or maintain alignment of the eyes and head as an organism orients itself and navigates the world.Past work has identified the superior colliculus (SC) as a generator of the motor command to drive saccades.Despite decades of research on the neural basis of saccades, we know very little about how the brain encodes the diverse range of kinematic features of saccades that naturally occur, because the majority of studies have used paradigms that elicit saccades with stereotyped trajectories.Here, we simultaneously record populations of SC neurons during a paradigm that induces saccades with a variety of amplitudes, start and end points, and velocities.Our results indicate that premotor SC neurons encode information about saccade kinematics at both a single unit and population level.We also identified two functional groups of premotor neurons: one that encodes eye position independently of saccades, and a second that encodes saccade kinematic features specifically.The electrophysiology results are corroborated by a set of experiments where we unilaterally, reversibly inactivated deep SC and observed direction-dependent changes in saccade frequency, along with shifts in eye position during and outside of saccades.Overall, this study reveals an important element of the neural basis for saccades with a wide rangeof kinematic features, which is crucial given the diversity of saccade trajectories that occur as we navigate the world.

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Poster

PSTR364: Eye Movements

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR364.06/Web Only

Topic: F.01. Eye Movements

Title: Effect of sports experience on changes associated with maintaining neck flexion in distribution of pro-saccade reaction time under gap task

Authors: *K. KUNITA[1], K. FUJIWARA[2], C. YAGUCHI[3], F. SATO[4];
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Abstract: The present study investigated the effect of sports experience on changes with maintaining neck flexion in distribution of pro-saccade reaction time under gap task. The subjects consisted of 15 participants each from basketball club group (BB group), table tennis club group (TT group), and non-sporting control group (C group). Pro-saccade overlap and gap

reaction tasks were carried out while maintaining neck rest and flexion positions. Reaction times were divided into 10-ms bandwidth for each neck position and saccadic task, and the histogram of the relative frequency for all trials was created. The median of the bandwidth in which the earliest peak appeared was calculated. Furthermore, the bandwidth showing the earliest peak in the histogram for the gap task at the neck rest position was set as the criterion bandwidth (0-ms), and the distribution of relative frequency was recalculated. The median of the bandwidth in which the earliest peak appeared was significantly shorter in the neck flexion position than in the neck rest position in both BB and TT groups for all tasks, but no significant change was observed in C group. In BB group, the distribution of reaction times in the gap task showed significant increase in the early component of bimodal distribution and a significant decrease in the late component, with maintaining neck flexion. In TT group, significant increase in the early, unimodal distribution was found, with maintaining the flexion. The results of this study indicated that sports experience leads to an earlier distribution of pro-saccade reaction time in the gap task, associated with the neck flexion position. Furthermore, it was suggested that this early in the distribution differed depending on the sport experienced.

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Poster

PSTR364: Eye Movements

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR364.07/DD12

Topic: F.01. Eye Movements

Support: ANR 24 CE92 0005 01
DGF project 545300591

Title: Kv1.1 vestibular neurons adjust eye velocity during angular VOR in larval frog

Authors: *M. PAIN[1], S. GLASAUER[2], D. CATTAERT[3], F. LAMBERT[4];
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Abstract: The angular vestibulo-ocular reflex (VOR) transforms sensory signals from head rotation detection by the semicircular canals into compensatory conjugate eye movements in order to minimize visual drift during gaze stabilization. In all vertebrates, the angular VOR is supported by a 3 neurons arc composed by vestibular sensory neurons (1rst order vestibular neurons; 1°VN), central vestibular neurons (2°VN) and extraocular motoneurons. This simple circuit is composed by distinct neuronal subtypes expressing different molecular and electrophysiological properties that build parallel pathways differently involved in the tuning of the angular VOR. In frog, 1° and 2°VN are subdivided in 2 distinct phenotypes, depending on the presence of the Kv1.1 channel. Kv1.1+ 1°VN and 2°VN present an irregular resting activity

and a phasic-adapting discharge, respectively. So far, the exact role of these vestibular neuronal phenotypes in the sensory-motor signal transformation of head rotations into compensatory eye movements remains unknown. To this aim, we combined videotracking, electrophysiology and computational modeling to investigate how Kv1.1+ 1°VN and 2°VN participate to the ocular kinematic during the angular VOR in larval frog. The blockade of Kv1.1 by bath application of 4-AP in semi-intact larval preparations did not change the VOR gain except for a small increase at 1Hz but elicited saccades and small amplitude perturbations of the eye velocity not present in the control condition. The 4-AP effect was stronger at low frequency than high frequency. Extracellular recording of the Abducens nerve during sinusoidal head rotations under 4-AP confirmed this first result by showing perturbated discharge modulation with the appearance of a chaotic resting activity during the VOR OFF phase of the recorded nerve without changing the peak discharge at the ON phase. We built a computational NEURON model to test the respective contribution of irregular afferent vestibular fibers and of phasic 2°VN on the Abducens nerve discharge, encoding for the eye velocity. Altogether, our results show that blocking Kv1.1+ vestibular neurons in larval frog provokes an angular VOR with an unstable eye velocity. Consequently, the role of Kv1.1+ neurons in the VOR 3 neurons arc circuit would be to continuously adjust eye velocity in order to minimize the retinal drift during compensatory eye movements elicited by head rotations. In mammalians, such a control of the ocular kinematic during VOR could be supported by the larger diversity of neuronal phenotypes expressed.

Disclosures: M. Pain: None. **S. Glasauer:** None. **D. Cattaert:** None. **F. Lambert:** None.

Poster

PSTR364: Eye Movements

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Program #/Poster #: PSTR364.08/DD13

Topic: F.01. Eye Movements

Support: Howard Hughes Medical Institute Freeman Hrabowski Laboratory Funding
E. Matilda Ziegler Foundation for the Blind

Title: Sensorimotor Innervation of Extraocular Muscles Varies with Oculomotor Complexity Across Species

Authors: E. KEMPKES[1], E. TUBBS[1], S. SARAF[1], M. RAYKOFF[2], E. SAVIER[2], *M. SEDIGH-SARVESTANI[3];
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Abstract: To make sense of visual inputs, the brain must know where the eyes are pointing in the orbit. How this eye position signal is generated remains an open question. Unlike limb muscles, the extraocular muscles (EOMs) of most species lack classical proprioceptive sensors, such as muscle spindles. It is debated whether the EOMs contribute sensory signals to the brain,

or if eye position is represented solely through motor efference copy (Donaldson 2000, Blumer et al. 2023). Palisade endings (PEs) — specialized structures found at the myotendinous junctions of EOMs — are one candidate source of sensory feedback, but their function as sensory, motor, or sensorimotor is unresolved. Adding to this uncertainty, PEs are not universal across species and are absent in most rodents (Blumer et al. 2016). This uneven cross-species distribution complicates interpretations of the role of PEs. Comparative data on oculomotor behavior may help resolve this question, as animals with finer control of their eye movements might require greater innervation of the EOMs. To test this hypothesis, we quantified PEs and eye-movement behavior in two similarly sized mammals with different visuomotor demands: rats (Rattus norvegicus) and tree shrews (Tupaia belangeri).

To identify PEs, we used histological approaches, mechanosensory markers, and confocal imaging across multiple EOMs. Labeled structures include axons (anti-neurofilament), synapses (anti-synaptophysin), muscle fibers (phalloidin), and slow-twitch muscle fibers (anti-MYH7). As a complementary dataset, we used video-oculography to quantify the degree to which rats and tree shrews can control their eye movements.

We quantified PEs in both the lateral (LR) and superior rectus (SR) EOMs of rats and tree shrews and found that PEs were present in both lateral-eyed species but were significantly more abundant and elaborate in tree shrews (tree shrew (n=2): LR=11±8.4, SR=2.8±3.8; rat (n=2): LR=0±0, SR=0.25±0.50). Preliminary observations also suggest the presence of PEs in the medial and inferior rectus muscles in both species. Tree shrews also exhibit increased eye movements, with a mean saccade rate of 55±12 per minute under head-fixation, compared to 1.4±1.2 per minute in rats.

The greater abundance and complexity of PEs in tree shrews — a highly visual species with more elaborate eye movements — suggests these structures play a meaningful role in oculomotor function, whether as sensory detectors, motor effectors, or as part of a sensorimotor feedback loop. Whether the EOMs contribute proprioceptive signals to the brain remains an open question that warrants further investigation.

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Poster

PSTR364: Eye Movements

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR364.09/DD14

Topic: F.01. Eye Movements

Support: Howard Hughes Medical Institute
E. Matilda Ziegler Foundation for the Blind

Title: Active vision in tree shrews: a lateral-eyed animal with a frontal view

Authors: *R. PAL, E. KEMPKES, R. AELETI, M. SEDIGH-SARVESTANI;
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Abstract: Tree shrews are an emerging model for visual neuroscience given their evolutionary proximity to primates and well-developed visual system, yet their active gaze behavior remains uncharacterized. Tree shrews are small and have lateral eyes. Other small, lateral-eyed mammals such as mice shift their gaze primarily by moving the head — because rotating a laterally placed eye adds little to the already wide monocular field of view and the low energetic costs of moving a small head make head turns the more effective strategy. However, tree shrews navigate complex arboreal environments demanding rapid, precise sampling of the visual scene, a challenge typically met by frontal-eyed primates through voluntary, head-independent eye movements. This raises the possibility that tree shrews break the frontal-eye/lateral-eye dichotomy by retaining a wide panoramic field of view for threat detection while exercising voluntary control over eye movements to covertly sample relevant parts of the visual field without moving the head. Consistent with this, their extraocular muscles revealed abundant sensorimotor innervation suggestive of fine motor control. To test the hypothesis that despite lateral orbits, tree shrews shift their gaze using head-independent eye movements, we used video oculography to record eye movements in 2 head-fixed tree shrews while measuring head acceleration associated with head-movement attempts with an accelerometer and force-sensor. We found that 94% of eye movements (n=72339) occurred with head acceleration indistinguishable from noise, demonstrating robust head-independent eye movements. For comparison, only 3% of eye movements in mice are head-independent (Meyer et al., 2018). To control for body size, we repeated experiments in rats and found 64% head-independent eye movements (n=652), albeit at a substantially lower rate than tree shrews (1.4±1.2 /min vs 54±12 /min). By contrast, stationary marmosets, a small frontal-eyed primate, make ~100 saccades/min (Singh et al., 2024). In a second set of experiments, we applied operant conditioning to determine whether tree shrews can voluntarily shift and hold gaze. Animals were rewarded for making a saccade to a randomly positioned visual target and maintaining fixation for 700 ms. Both animals learned the task with an average success rate of 72% and median latency of 2.7 s (IQR 0.91 - 4.4) (5 sessions per animal, n = 104 trials), demonstrating active gaze control using eye movements alone. Our findings suggest that lateral-eyed tree shrews are capable of actively sampling the visual world using eye movements, reminiscent of strategies used by frontal-eyed primates despite having lateral eyes.

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Poster

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NIH NEI R01NS147766
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Title: Serial dependence of spatial working memory in a mixed eye movement task

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Abstract: Serial dependence of working memory describes a phenomenon where memories of current stimuli are biased by previously seen stimuli. In behavioral tasks, this often manifests as an attractive bias towards the previous trial's response. While serial dependence in eye movements has typically been analyzed in tasks that focus on only one type of eye movement (e.g., saccades or smooth pursuit), different types of eye movements frequently interact in everyday behavior. Thus, it is an open question as to how serial dependence manifests in a more naturalistic eye movement task that involves different types of interspersed eye movements. To address this issue, we used an infrared eye tracker to record eye movement behavior from one rhesus macaque performing three tasks: a conventional memory-guided saccade task, a conventional step-ramp ("Rashbass") smooth pursuit task, and an interleaved memory-guided saccade and smooth pursuit task. Analysis of the memory-guided saccades and pursuit tasks performed in separate tasks yielded serial dependence effects consistent with prior work in macaques (Papadimitriou et al., 2015; Darlington et al., 2017). In the isolated memory-guided saccade task, eye movements were angularly biased towards the previous saccade. In the isolated smooth pursuit task, eye movement velocity was biased towards the velocity of the previous trial's pursuit velocity. Using the interleaved memory-guided saccade and smooth pursuit task, we found a memory-guided saccade attractive angular bias in consecutive saccade-saccade trials, consistent with the isolated task results. Preliminary results suggest that consecutive pursuit-saccade trials also have an attractive angular bias. These results suggest that serial dependence effects are present across movement subtypes in the oculomotor system.

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Poster

PSTR364: Eye Movements

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T32EY017271

Title: Mixed oculomotor signals in the primate frontal eye fields

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Abstract: Natural visual behavior depends on the transformation of incoming visual information into coordinated eye movements. This process is complicated by the unpredictability of the visual environment. For example, to follow a moving target such as a fly darting across a room, primates mainly rely on two complementary oculomotor strategies: fast, discrete saccades to redirect gaze and slower smooth pursuit to continuously track the motion trajectory. Although the ability to seamlessly alternate between these strategies implies that the underlying sensorimotor systems are tightly coupled, they have largely been studied in isolation and are thought to be driven by functionally distinct brain circuits in the frontal eye fields (FEF). Thus, it is unclear how visual, saccadic, and pursuit signals are collectively represented in individual neurons in FEF. To address this issue, we used high-density Neuropixel probes to simultaneously record spiking activity from hundreds of FEF neurons while macaques performed a memory-guided saccade task and a pursuit task. These tasks allowed us to classify individual neurons along a continuum based on their relative visual-saccade-pursuit responsiveness. In contrast to the separable distributions predicted by functionally distinct circuits, FEF neurons formed a continuous distribution of mixed visual-saccade-pursuit responsiveness. Saccade selectivity was inversely related to visual and pursuit responsiveness such that neurons that were less saccade-selective exhibited greater visual and pursuit-related activity and vice versa. This result was consistent across animals and recording sites and not an artifact of neuronal isolation or recording quality. Neuron pairs with similar visual-saccade-pursuit response profiles had stronger trial-by-trial correlated variability during their preferred epoch. However, even highly task-selective pairs exhibited positive correlated variability during their non-preferred epochs, suggesting weak but widespread functional coupling across the FEF population. Mixed visual-saccade-pursuit neurons comprised the majority of the recorded population and exhibited broader direction tuning relative to task-selective neurons. We also tested the impact of their removal from population activity using cross-task decoding. Together, these findings demonstrate the extent to which visual, saccade-, and pursuit-related signals overlap within FEF, which appears to be considerably more than previously thought. More broadly, our work suggests that a heterogeneity of neural representations, rather than a segregated abstract code, supports the flexible coordination of gaze.

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Poster

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Topic: F.01. Eye Movements

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Title: Independent eye signals during saccades revealed by neurotypical phorias

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Abstract: Saccades are thought to be driven by a single command, a belief depicted by models of saccade control. We challenge this idea by taking advantage of a well-known clinical phenomenon known as phoria. A phoria occurs when an eye is covered during fixation, and that eye deviates either inward or outward from its viewing position. Phorias occur in most people and are usually present in both eyes but occasionally become pathological in which case the deviation progresses in magnitude to eventually manifest as strabismus. Because covering an eye in normals reveals the phoria, we hypothesize that when uncovered, the oculomotor system must continuously generate an independent signal to align that eye with a target. If so, models that drive binocular eye movements using unitary neural signals (conjugate or vergence) could be incorrect. To determine if independent signals persist during normal saccade generation, we measured both eyes as observers repeatedly made horizontal or vertical saccades during binocular and monocular viewing. The target was a small (.2 deg) white dot presented on a uniform grey background. Each trial began with a randomized (1-1.5 sec) fixation period during which the static phoria was assessed. For monocular viewing, an eye was occluded with an infrared pass filter to allow binocular eye movement recording (Eyelink 1000+ eye tracker). Under binocular viewing, as expected both eyes moved together as a pair. Under monocular viewing for horizontal saccades, the fixation-phoria in the covered eye was maintained, keeping the eyes horizontally displaced during the saccade. However, saccade magnitudes in the eyes remained the same. For vertical saccades the covered eye was also displaced horizontally while vertical alignment was maintained. The results suggest that a unitary signal drives both eyes during saccades, but independent control signals driven by vision correct each eye's phoria during binocular viewing.

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Poster

PSTR364: Eye Movements

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Topic: F.01. Eye Movements

Support: NIH Grant T32-EY007043

Title: Beyond random walks: how systematic and random components of drift eye movements are modulated by viewing condition

Authors: *E. C. REHOR, J. OTERO-MILLAN;
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Abstract: Fixational drift—the slow eye movement occurring during fixation—is commonly characterized as a random process, despite evidence that it also contains a systematic bias component. In this work, we sought to quantify both the random and systematic components of drift in order to provide a more comprehensive account of its dynamics. We recorded binocular eye movements from head-fixed participants during sustained fixation and free viewing of natural scenes (n = 8) using dual-Purkinje imaging (DPI) within the OpenIris framework. Across subjects, drift velocity exhibited significant position dependence in the vertical direction during both sustained fixation (−0.24 ± 0.24 arcmin/s/deg) and free viewing (−0.72 ± 0.66 arcmin/s/deg), and in the horizontal direction during free viewing (−0.48 ± 0.42 arcmin/s/deg). Significant position-independent vertical biases were also observed during fixation (−6.48 ± 6.96 arcmin/s) and free viewing (−8.46 ± 7.74 arcmin/s). Vertical position-dependent bias was stronger during free viewing than fixation ($t(7) = 3.31$, $p < 0.05$), while position-independent bias showed a similar trend ($t(7) = 2.23$, $p = 0.06$). To quantify the random component, we removed each subject's systematic bias from the eye movement data and calculated the diffusion constant (d) of the residual motion at central viewing. The diffusion constant during free viewing was significantly greater than during sustained fixation ($t(7) = -2.41$, $p < 0.05$). Removing the systematic component reduced d by an average of 24% across conditions, indicating that systematic biases make a substantial contribution to conventional diffusion estimates. These findings demonstrate that fixational drift can be described by two distinct components—systematic and random—both of which contribute substantially to its overall dynamics. Furthermore, both components were sensitive to viewing condition. Specifically, free viewing was associated with a stronger vertical position-dependent velocity bias than sustained fixation, as well as increased diffusion constant at central viewing. Future studies characterizing fixational drift should therefore account for both its systematic and random components in order to accurately represent its dynamics.

Disclosures: E.C. Rehor: None. **J. Otero-Millan:** None.

Poster

PSTR364: Eye Movements

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Program #/Poster #: PSTR364.14/DD19

Topic: F.01. Eye Movements

Title: A virtual eye-movement laboratory: a whole-system model of human oculomotor control for teaching and synthetic-data generation

Authors: *J. OTERO-MILLAN;
Univ. of California Berkeley, Berkeley, CA

Abstract: Eye movements are a sensitive, quantifiable window into neurological disease: focal brainstem, cerebellar, and vestibular lesions produce characteristic signs that clinicians use to localize pathology at the bedside. Yet these signs can be hard to teach and quantify, and most computational models capture a single behavior—saccades, the vestibulo-ocular reflex (VOR), or vergence—in isolation, limiting their use for teaching or for generating data to constrain automated-diagnosis pipelines. We present a virtual eye-movement laboratory: a unified simulator of the human oculomotor system that reproduces the full repertoire of eye movements within a single architecture and parameter set, in which focal lesions reproduce clinical syndromes.
Rather than fitting each behavior separately, a single biophysically grounded parameter set governs the whole system—from the vestibular and visual periphery through the brainstem, neural integrator, and cerebellum to a binocular plant—so that reflexive stabilization, voluntary gaze shifts, and binocular alignment all emerge from one circuit and quantitatively match the classic benchmarks of each. Because every component maps onto an identifiable neural structure, lesioning a pathway reproduces the corresponding clinical syndrome, from internuclear ophthalmoplegia to gaze-evoked nystagmus. Every parameter corresponds to a specific physiological quantity—time constants, gains, and lesion strengths—so the model is mechanistically interpretable and can be fit to recorded eye movements. Because any stimulus can be applied to any healthy or lesioned subject, the laboratory serves two roles. First, the model is distributed with a companion website on which a user simply types a scenario in plain language (e.g., "left vestibular neuritis during a head-impulse test"); the site configures the corresponding experiment and patient, runs the simulation, and returns annotated figures, letting students and clinicians explore normal and pathological eye movements without writing code. Second, it generates synthetic data: responses simulated under known parameters and noise yield labeled datasets for validating parameter-recovery and disease-classification methods before use on patient data.

Disclosures: J. Otero-Millan: A. Employment/Salary (full or part-time):; UC Berkeley.

Poster

PSTR364: Eye Movements

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Topic: F.01. Eye Movements

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Title: Nucleus prepositus neurons carry eye- and gaze-related signals during voluntary orienting in mice

Authors: *B. M. VERDONE[1], M. GREEN[2], A. CHENG[2], T. HARRIS[3], K. E. CULLEN[1]; [1]Biomed. Engin., [2]Johns Hopkins Univ., Baltimore, MD; [3]HHMI JRC, Ashburn, VA

Abstract: Animals use coordinated eye and head movements to redirect gaze, sample the environment, and update internal estimates of spatial heading. In the canonical model, angular head velocity signals are thought to flow from vestibular afferents through the medial vestibular nucleus (MVN) and nucleus prepositus hypoglossi (NPH) to the dorsal tegmental nucleus (DTN), an essential component of the head direction network. Thus, NPH has often been assumed to relay head-velocity signals that update the head direction compass. However, this assumption stands in contrast with NPH's conserved role as an oculomotor integrator supporting both saccadic and reflexive eye movements, raising the possibility that signals transmitted through this pathway include significant eye-related information. To address this possibility, we recorded from NPH using high-density Neuropixels 2.0 probes while simultaneously tracking head and eye position in mice. We previously identified eye-sensitive units using passive gaze-stabilization tasks: static eye position (SEP), in which discrete rotations elicited different orbital eccentricities, and the vestibulo-ocular reflex (VOR), in which sinusoidal head rotations elicited compensatory eye movements. Eye-sensitive units were defined as those whose firing rates were modulated during both tasks in a manner consistent with eye-position or eye-velocity sensitivity. We then asked whether these identified eye-sensitive units also carry eye- and gaze-related signals during voluntary orienting. To test this, we recorded neural activity in body-restricted, head-free mice (N=4) performing a voluntary gaze-redirection task, in which animals made self-initiated head turns between reward ports. Neural activity during active orienting was compared with activity during comparable passive head motion. During voluntary orienting, NPH neurons robustly modulated their firing around active gaze shifts. Model comparisons identified units whose activity was better explained by eye position and eye velocity than by head movements alone. Together, these findings show that eye-related signals in NPH generalize from passive gaze-stabilization tasks to voluntary orienting, suggesting that this ascending brainstem pathway carries oculomotor information during active gaze redirection.

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Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

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Program #/Poster #: PSTR365.01/DD21

Topic: F.02. Cerebellum

Support: JSPS KAKENHI (25KJ2243)

Title: A split-wheel treadmill as a behavioral paradigm for studying locomotion adaptation in head-fixed mice

Authors: *A. GAVRILOVA, B. KUHN;
OIST, Okinawa, Japan

Abstract: Locomotion adaptation enables animals to maintain a stable gait under changing environmental conditions and critically depends on cerebellar function. Split-belt treadmills are a widely used experimental paradigm for studying locomotion adaptation by imposing different speeds on the left and right sides of the body. However, the neural mechanisms underlying this process remain poorly understood due to the limited compatibility of existing split-belt paradigms with high-resolution neural recordings. Here, we developed a motorized split-wheel treadmill for head-fixed mice that enables simultaneous behavioral monitoring and two-photon calcium imaging during locomotor adaptation. The system consists of two transparent wheels independently controlled by servo motors, a compact head-fixation apparatus, and a bottom-view imaging system for capturing multi-limb kinematics. In a three-day experimental setting, we concurrently recorded the locomotion and two-photon calcium imaging of Purkinje cell (PC) dendrites in cerebellar lobules IV/V of head-fixed L7-Cre mice expressing GCaMP8f. We observed that mice exhibited robust adjustments in all four limbs characterized by changes in stride length, step length, center of oscillation, and double support asymmetries across days. To examine the global structure of locomotor coordination, we applied principal component analysis (PCA) to all four limbs kinematics, thereby reconstructing its low-dimensional state-space trajectory. The first three components of PCA revealed a condition-dependent reorganization of the limbs movement patterns during transitioning between baseline and split phase as well as between split and washout phase. Importantly, we observed that whereas the overall low-dimensional structure of the locomotion was preserved, the geometry of the PCA trajectory changed substantially by exhibiting phase-dependent reorganization of the kinematic manifolds. This was particularly evident during the split-wheel walking, indicating modifications of the inter-limb coordination. These results suggest that observed adaptive remodeling associates with the locomotor dynamics rather than changes to movement dimensionality. To validate our observation, we aim to determine how PC dendritic activity relates to the changes in state-space structure during gait adjustments. Together, our results establish a novel understanding of the neural mechanisms underlying cerebellar-dependent locomotion adaptation.

Disclosures: A. Gavrilova: None. **B. Kuhn:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR365.02/DD22

Topic: F.02. Cerebellum

Support: NIH/IRP ZIA NS009434-04
NINDS NCFA

Title: Granule cells reorient cortical trajectories to separate contexts but preserve their geometry

Authors: *M. G. GARCIA GARCIA[1], S. THOTA[2], O. AKINWALE[3], L. RAMOS[1], R. COSTA[4], M. WAGNER[1];
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Abstract: To learn effectively, animals must generalize across yet distinguish between related contexts. Generalization relies on low-dimensional neural manifolds found throughout neocortex, which accelerate learning by constraining neural activity to task-relevant axes. Conversely, context separation is attributed to neural expansion layers that can project information into high-dimensional feature spaces, most famously cerebellar granule cells (GrCs), which outnumber all other neurons in the brain combined. To investigate the generalization-separation tradeoff, we simultaneously imaged key nodes in the universal cortico-cerebellar pathway—premotor layer 5 pyramidal tract (L5PT) and GrCs in Crus I, II and Simplex—during parallel learning of two distinct skills with shared temporal structure: a reach-for-reward task and a run-for-reward virtual reality task. Using a custom dual-site two-photon microscope, we longitudinally tracked L5PT and GrC populations, which are disynaptically connected through the pons. We found that, rather than expanding the cortical representations into a high-dimensional feature space, GrCs retained their low-rank encoding of each task. Across contexts, L5PT activity patterns generalized while GrC patterns temporally remapped, despite stable cortico-cerebellar coupling. Interestingly, GrC populations remapped coherently: their low-dimensional trajectories “rotated” apart between tasks, separating contexts while preserving the cortical geometry of each. Moreover, GrC trajectories diverged most strongly in expert mice, confirming the role of GrCs in context separation for effective dual-task learning. Finally, a simulation of dual-task learning in a cerebellar microcircuit confirmed that rotation of low-dimensional cortical trajectories optimizes rapid learning while minimizing interference. Our findings suggest a fundamental architectural division of labor: the cortex provides invariant dynamic primitives for smooth generalization, while cerebellar activity reconfigures them to drive context-specific output.

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Poster

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Topic: F.02. Cerebellum

Support: NS134561
NS141896

Title: Cerebellar granule cells form a flexible activity representation of kinematic features of rodent reach-to-grab tasks

Authors: K. NGUYEN[1], S. SCHAMILOGLU[2], ***A. L. PERSON**[2], D. A. DIGREGORIO[3]; [1]Univ. of Colorado, Aurora, CO; [2]Physiol. and Biophysics, Univ. of Colorado, Anschutz Med. Campus, Aurora, CO; [3]Physiol. and Biophysics, CU Sch. of Medicine, Anschutz Sch. of Med., Aurora, CO

Abstract: A long-standing theoretical framework posits that cerebellar granule cells (GCs) represent discrete moments in time, a feature critical for precise movements. These diverse activity patterns could be used as a basis set by downstream circuits to generate precisely timed motor commands. While temporally diverse GC activity patterns have been observed during sensory stimuli, locomotion, and reward delay periods, it is unknown whether GC basis sets exist during learned movements and are sufficiently reliable and temporally diverse as predicted by models of motor adaptation. We leveraged simultaneous high-speed two-photon GCaMP8f calcium imaging of GC activity in lobules IV/V and high-dimensional markerless tracking while mice performed a skilled reaching task. We first analyzed whether GCs tiled the reach epoch. 134 GCs had a peak calcium transient within a 1 second window centered around reach peak velocity. Sequential GC peak times of trial averaged transients occurring within this interval differed by 13.9 ± 10.5 ms (n = 134, 2 mice). Additionally, cross-validated trials showed 92 ± 4% of GCs had correlations exceeding $r > 0.8$, indicating they reliably tiled the movement. Calcium transient durations were heterogeneous across cells (FWHM 330 ms-3.1s), indicating a temporally diverse GC representation of behavioral features. Reaching recruited larger GC populations than whisker air-puff stimulation, activating 11-28% of imaged GCs (n = 283) compared with 2% in Crus I during sensory stimulation (Bender, Sermet et al., bioRxiv, 2026). Despite denser recruitment, reaching drove high dimensionality, consistent with a recent study examining locomotion: principal component analysis revealed that the first 26-33 principal components explained 80% of the variance. To further examine the GC population kinematic representations, we recorded GC activity during reaches to two distances. We were surprised to see, rather than two distinct populations of active GCs, a subset (23-67%) of GCs were active during both near and far reaches. However, GCs transients were larger during far than near reaches (26.3 ± 0.9% vs 17.1 ± 0.1% dFF, $p < 0.001$) suggesting increased firing rates during farther movements. These results suggest that two different behaviors can be distinguished by GC firing rates. Our findings extend the Marr-Albus framework: different motor outputs can be generated by differences in GC firing rate, not just by which GCs fire or when.

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Poster

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Title: Complex Spike Coding Distinguishes Predictive Reafference Suppression from Context-Invariant Self-Motion Encoding in Macaque Cerebellar Vermis

Authors: *C. BAO[1], R. L. MILDREN[2], K. E. CULLEN[3];
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Abstract: During voluntary movement, the nervous system must both suppress predictable sensory feedback that would drive counterproductive reflexes and preserve accurate sensory estimates needed for balance, posture, and spatial orientation. The cerebellar vermis contains circuitry positioned to support these complementary computations. Prior work has shown that Purkinje cell simple spikes in the anterior vermis are attenuated during active compared with passive head motion, consistent with predictive reafference suppression in downstream deep cerebellar and vestibular nuclei pathways. In contrast, Purkinje cells in the posterior vermis/nodulus-uvula maintain comparable simple spike responses during active and passive movements, consistent with a context-invariant, ground-truth representation of self-motion and orientation relative to gravity. However, whether climbing fiber input follows this same regional organization remains unknown. Here, we recorded 103 Purkinje cells with well-isolated complex spikes from the anterior and posterior vermis of three alert rhesus monkeys during passive and voluntary self-motion. In the anterior vermis, complex spike responses were strongly attenuated during voluntary head movements compared with kinematically matched passive motion, paralleling simple spike attenuation and consistent with predictive suppression of self-generated sensory input. In contrast, posterior vermis complex spike responses were comparable during active and passive motion, indicating that climbing fiber input to this region preserves self-motion signals regardless of movement context. Across both regions, complex spikes were precisely time-locked to unexpected vestibular or proprioceptive stimulation and showed reciprocal temporal organization with simple spikes but conveyed less detailed kinematic information than simple spike firing rates. Together, these findings reveal a regional specialization in cerebellar climbing fiber signaling: anterior vermis complex spikes participate in context-dependent attenuation of self-generated motion signals, whereas posterior vermis complex spikes preserve the context-invariant sensory information needed to maintain a veridical estimate of self-motion and orientation in space.

Disclosures: C. Bao: None. **R.L. Mildren:** None. **K.E. Cullen:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.05/DD25

Topic: F.02. Cerebellum

Support: NIH R37-NS128416
NIH R21-NS145008

Title: Climbing fiber input encodes the gradient of a reward-dependent loss function for the cerebellum

Authors: *J. DOOSTMOHAMMADI[1], N. MOHAMMADREZAEI[2], H. Y. ELSEWEIFI[3], A. CHANDLER[5], R. SHADMEHR[4];
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Abstract: Learning aims to minimize loss, a scalar function that measures how well an action is performed. For example, when a tennis serve misses its target, the loss associated with the error is greater at match point than during practice. Thus, when a movement produces an error, the resulting learning should depend on both the sensory properties of the error and the reward context in which it occurred. Is there a teaching signal in the brain that combines these two sources of information? In machine learning, backpropagation provides such a signal by computing the gradient of loss with respect to each neuron's output. This gradient combines the sensitivity of loss to error, which depends on reward context, with each neuron's contribution to error. The success of backpropagation suggests that a biological teacher cannot simply broadcast errors. Instead, it must combine sensory error and reward context with each neuron's contribution to behavior. We investigated whether cerebellar climbing fibers convey teaching signals consistent with the gradient of a reward-dependent loss function. We trained marmosets to associate targets with different rewards and manipulated errors and reward outcomes using intersaccadic target jumps and reward-value changes. Behavioral analyses revealed that trial-to-trial adaptation followed endpoint error and was strongly modulated by reward context, with learning enhanced when obtained reward exceeded expectation and reduced when reward fell below expectation. We recorded complex-spike activity from 906 Purkinje cells in cerebellar vermis lobules VI-VII. Climbing fibers encoded the direction and magnitude of visual and motor errors, while reward value multiplicatively scaled these responses. Cells that strongly encoded target direction also encoded target value, and reward information emerged ~25 ms after directional information. To test whether these signals reflected the gradient of a loss function, we measured each Purkinje cell's potent vector using spike-triggered averaging. Climbing fiber activity was proportional to the projection of a reward-dependent error vector onto the cell's potent vector, reaching a maximum when the vectors were aligned and remaining near baseline when orthogonal. These findings demonstrate that climbing fibers combine sensory prediction errors and reward-related signals to generate cell-specific teaching signals that solve the credit assignment problem, providing evidence that cerebellar learning implements a biologically plausible form of gradient descent.

Disclosures: J. Doostmohammadi: None. **N. Mohammadrezaei:** None. **H.Y. Elseweifi:** None. **A. Chandler:** None. **R. Shadmehr:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.06/DD26

Topic: F.02. Cerebellum

Support: NIH R01 NS072406
NIH R01 DC004154

Title: Interactions Between Successive Climbing Fiber Activations in Shaping Cerebellar Long-Term Plasticity

Authors: *F. SAYEHMIRI[1], J. L. RAYMOND[2];
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Abstract: The direction and magnitude of plasticity at parallel fiber (PF)-Purkinje cell synapses in the oculomotor cerebellum depend critically on the precise timing of climbing fiber (CF) activation relative to PF input. Here, we investigate how a second CF activation interacts with a PF+CF pairing that induces long-term depression (LTD) to shape the plasticity outcome. Whole-cell patch-clamp recordings were used to measure LTD at the PF-Purkinje cell synapses in slices of the cerebellar flocculus from wild-type mice. Our lab showed previously that LTD at these synapses is selectively induced by a PF-CF pairing interval of 120 ms. Using 120 ms as our LTD-inducing reference interval, PF stimulation was paired with two CF activations delivered at systematically varied intervals. We first determined whether adding a CF stimulation at 100 ms, an interval that, on its own, induces long-term potentiation (LTP), suppresses, reverses, or leaves intact the LTD produced by the 120 ms pairing. Then we tested whether the temporal order of the two CF activations matters by comparing conditions in which the LTP-inducing CF activation precedes versus follows the LTD-inducing CF activation time of 120 ms. Finally, motivated by prior evidence suggesting that temporal summation of CF signals can support LTD induction, we tested whether two CF activations that individually fail to induce LTD, such as at 100 and 150 ms, can drive LTD when delivered together after PF activation. Preliminary results suggest that all three of the double climbing fiber activation protocols can induce LTD. The results advance our understanding of the timing rules that govern cerebellum-dependent learning by revealing how the cerebellum integrates climbing fiber signals to compute a net plasticity outcome.

Disclosures: F. Sayehmiri: None. **J.L. Raymond:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.07/DD27

Topic: F.02. Cerebellum

Support: NIH Center for Compulsive Behaviors Graduate Student Fellowship

Title: Functional heterogeneity of Purkinje cell reward responses

Authors: *B. A. FILIO, III[1], M. J. WAGNER[2];
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Abstract: Increasing evidence couples the cerebellum to higher cognitive functions, such as in reward-motivated behavior. Studies show that cerebellar granule cells and climbing fiber inputs convey predictive and instructive reward signals respectively, yet it is relatively unclear how Purkinje cells (PkCs), which receive these inputs, process them to influence downstream cerebellar computations. Further, it is classically known that PkCs are functionally organized along microzones, yet how these microzones differentially compute reward parameters is unclear. To parse out PkC reward-related computations, we used 2-photon calcium imaging to record PkC dendritic and somatic activity from Lobule VI and Crus I/II while mice performed an operant task for stimulation of the medial forebrain bundle. This study will provide further clarification on how reward information is encoded and transformed by PkCs, particularly their simple spiking activity and microzone organization.

Disclosures: B.A. Filio: None. **M.J. Wagner:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.09/DD29

Topic: F.02. Cerebellum

Support: NiH Grant DC002390
NIH Grant DC018061
Raynor Cerebellum Foundation
Kavli Neuroscience Discovery Institute Distinguished Postdoctoral Fellowship

Title: Cerebellar fastigial nucleus output generates context-dependent head stabilization responses in primates

Authors: *R. L. MILDREN[1], B. TSENG[2], T. HARRIS[3], A. CHARLES[4], K. E. CULLEN[5]; [1]Biomed. Engin., [2]Johns Hopkins Univ., Baltimore, MD; [3]HHMI JRC, Ashburn, MD; [4]Johns Hopkins Univ. - Homewood Campus, Lutherville-Timonium, MD; [5]Dept. of Biomed. Engin., The Johns Hopkins Univ., Baltimore, MD

Abstract: The cerebellum plays a crucial role in postural control, as demonstrated by severe balance impairment in individuals with spinocerebellar ataxia. The cerebellar vermis is essential for maintaining postural stability by integrating vestibular with other sensorimotor signals to encode self-motion and transform these signals into appropriate motor commands. Purkinje cells in the vermis converge onto neurons in the vestibular and fastigial nuclei, which relay cerebellar output to downstream postural control pathways. Although prior work has elucidated roles of the anterior vermis and rostral fastigial nucleus in signaling head and body motion, what this output does for postural control remains unknown. Here, we tested the hypothesis that rostral fastigial output contributes causally to head-neck stabilization during voluntary movement.

We inserted high-density silicon recording/stimulation electrodes in the rostral fastigial nucleus, targeting neurons that encode unexpected head motion. We recorded neural activity in two rhesus monkeys while they made voluntary yaw head rotations between two juice spouts located ~45° from center. Using closed-loop microstimulation (400Hz, 100ms duration) triggered by head velocity, we found that stimulation induced a head stabilization response, arresting movement before the monkey reached the target. Stimulation during ipsilateral movement produced target undershoot relative to control (-21.5±13.1 vs -3.4±10.5 deg, $p<0.001$) and reduced average movement speed (114±27 vs 129±17 deg/s; $p<0.001$), reflecting premature termination of the ongoing head movement and requiring an additional corrective movement to reach the target. Importantly, we observed no ataxia-like effects such as an oscillation or tremor ($p=0.761$). Interestingly, the same undershoot effect occurred regardless of movement direction. This is notable because activating the same muscle group would predict overshoot in one direction and undershoot in the other; instead, fastigial output generated symmetric stabilization. Stimulation at rest produced minimal motor response, demonstrating context-dependence. When we applied stimulation at different movement phases, the stabilization response timing shifted accordingly. Finally, repeated stimulation over 100 trials produced no adaptation, suggesting that the evoked stabilization response was stable across repeated perturbations.

These findings establish that rostral fastigial output generates robust context-dependent head-neck stabilization responses during movement, revealing a neural mechanism by which the cerebellum actively maintains postural control.

Disclosures: R.L. Mildren: None. **B. Tseng:** None. **T. Harris:** None. **A. Charles:** None. **K.E. Cullen:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.10/DD30

Topic: F.02. Cerebellum

Support: Raynor Cerebellum Project

Title: Cerebellar anterior interposed nucleus stimulation modulates movement kinematics and reshapes motor cortical activity during primate reaching

Authors: *N. LEBEDZ[1], R. L. MILDREN[1], B. TSENG[1], T. HARRIS[2,1], A. CHARLES[1], K. E. CULLEN[1];
[1]Biomed. Engin., The Johns Hopkins Univ., Baltimore, MD; [2]HHMI JRC, Ashburn, MD

Abstract: Skilled reaching depends on coordinated interactions between the cerebellum and cortical motor circuits. Although cerebellar output is known to influence motor cortex through cerebello-thalamo-cortical pathways, how cortical dynamics are modulated by deep cerebellar nuclei during reaching remains unknown. The anterior interposed nucleus (IntA) is an important cerebellar region for controlling reach kinematics. To understand its role, we stimulated in IntA, simultaneously recording from IntA and motor cortical areas, and tracked right-arm reaching kinematics.

We recorded from ipsilateral IntA using a prototype 128-channel read-write Neuropixels probe while simultaneously recording from contralateral motor cortical areas using four 64-channel Utah arrays implanted in the primary motor cortex (M1 inferior, M1 superior), dorsal premotor cortex (PMd), and supplementary motor area (SMA) as a rhesus monkey performed targeted reaching movements. During unstimulated trials, cortical activity followed the expected temporal pattern: PMd and SMA activity increased before movement onset, whereas M1 activity was most prominent during movement execution. Neurons in IntA were modulated during movement, primarily increasing their firing near reach endpoint. IntA stimulation across multiple channels with cathodic-first, biphasic, charge-balanced pulses evoked an increase in firing rates across many cortical channels during stimulation, followed in some channels by transient post-stimulation suppression before return to baseline. IntA units also showed brief excitation or suppression followed by recovery to baseline.

Behaviorally, IntA stimulation produced parameter-dependent changes in reach kinematics. 40-pulse stimulation trains at 400 Hz induced brief pauses in arm movement and increased movement duration (+150-300ms) without consistently affecting endpoint precision. Stimulation with significantly fewer pulses only evoked cortical responses with no noticeable behavioral effect. These effects were consistent across many sessions.

Our results demonstrate the feasibility of simultaneous cerebellar-cortical recording and stimulation during skilled reaching in macaques. They further show that perturbing IntA output can rapidly reshape motor cortical firing while selectively altering the kinematics of reaching movements. Together, these findings establish a framework for causally linking cerebellar output to motor cortical dynamics and for developing closed-loop stimulation strategies that shape movement timing during skilled action.

Disclosures: N. Lebedz: None. **R.L. Mildren:** None. **B. Tseng:** None. **T. Harris:** None. **A. Charles:** None. **K.E. Cullen:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.11/EE1

Topic: F.02. Cerebellum

Support: Israel Science Foundation

Title: Voltage imaging reveals functional divergence of forward and inverse models in the cerebellum

Authors: *S. ZADKA[1], M. HIBI[3], H. BAIER[4], T. KAWASHIMA[2];
[1]Dept. of Brain Sci., [2]Weizmann Inst. of Sci., Rehovot, Israel; [3]Dept. of Biol. Sci., Grad. Sch. of Science, Nagoya Univ., Nagoya, Japan; [4]Genes - Circuits - Behavior, Max Planck Inst. of Neurobio., Planegg, Germany

Abstract: During behavior, the cerebellum stores and updates internal models that link motor commands to their expected sensory consequences. Inverse models contribute to the generation of motor commands, whereas forward models predict the sensory consequences of actions and enable error computation when a mismatch occurs between predicted and actual sensory input. How these internal models are computed remains largely elusive, owing to long-standing challenges in studying cerebellar circuits. Here, we applied voltage imaging to the cerebellum of larval zebrafish to record neural activity from hundreds of Purkinje cells and granule cells during sensorimotor coupling and decoupling tasks. By analyzing membrane potential dynamics and simple- and complex-spike patterns, we identified distinct Purkinje cell subpopulations corresponding to inverse models, which encode future swim vigor, and forward models, which encode negative images of the expected optic flow during swimming. These two subpopulations exhibited distinct neural dynamics in their behavioral context dependence and plasticity during behavioral adaptation. In contrast, cerebellar granule cells, which provide direct input to Purkinje cells, showed mixed activity features and lacked clear error computations. This functional divergence between Purkinje cells and granule cells depended on the cerebellum-enriched metabotropic glutamate receptor 1 (mGluR1). Blocking mGluR1 impaired internal model computations and rendered Purkinje cell activity more explainable by feedforward inputs from granule cells. These results indicate that forward and inverse models become distinct at the Purkinje cell layer of the cerebellum through highly nonlinear computations, opening new opportunities to uncover the mechanistic underpinnings of cerebellar internal models.

Disclosures: S. Zadka: None. **M. Hibi:** None. **H. Baier:** None. **T. Kawashima:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.12/EE2

Topic: F.02. Cerebellum

Support: NIH DIR

Title: Probing corticopontine adaptation for cerebellar learning by all-optical methods

Authors: *Y. LIU, S. SRINIVASAN, D. RANA, M. WAGNER;
NINDS, NIH, Bethesda, MD

Abstract: Many higher cognitive functions, such as learning a new skill, require the involvement of both the neocortex and cerebellum. In all mammals, cortical information is transmitted to the cerebellum via the neocortex Layer 5 (L5) - Pontine Nuclei (PN) -cerebellar Granule Cells (GrCs) circuit. This pathway forms a bottleneck: L5 neurons substantially outnumber PN neurons, which are again drastically outnumbered by downstream GrCs. Thus, not all cortical information can transit through the PN. This raises a fundamental question about this conserved pathway: how do the PN select which cortical information to transmit to the cerebellum, and which to discard or attenuate? To date, it has not been possible to address this question due to the difficulty of causally probing neural information transmission between distant brain regions in behaving animals. Thus, we have developed an all-optical dual-site two-photon microscopy approach. With this technique, we can simultaneously and longitudinally record activity in the L5-PN-GrC pathway, as well as stimulate specific sets of individual L5 neurons, repeatably across learning. To validate this methodology, we first demonstrated simultaneous imaging of dense populations of GrCs and PN axon terminals using two-color imaging. In animals performing an operant behavior, we found ramping activity of GrCs and PN axons during motor planning. Next, we evaluated the effects of L5 stimulation on GrCs. We activated L5 cells via bulk optogenetic stimulation while imaging GrCs. We found a significant increase in the average calcium activity in GrCs, with some regions repeatedly showing response following each stimulation. To improve our all-optical system, we have scaled up our holographic stimulation system, streamlined our setup steps, and developed a system to rapidly generate L5 stimulation patterns based on observed cortico-cerebellar neural dynamics. These improvements position us to test our central hypothesis: that the cortico-PN circuit selectively transmits the most task-relevant information for downstream cerebellar learning.

Disclosures: Y. Liu: None. **S. Srinivasan:** None. **D. Rana:** None. **M. Wagner:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.13/EE3

Topic: F.02. Cerebellum

Support: Whitehall Foundation
Chan Zuckerberg Initiative
Research Corporation for Science Advancement

Title: Cerebellar encoding of temporal expectation signals during behavior

Authors: *S. AMINNAJI, J. ZHU, F. NAJAFI;
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Abstract: The cerebellum is a key node in the neural circuits underlying motor timing and adaptation, processes that rely on temporal expectation. Climbing fiber inputs to Purkinje cells are thought to convey prediction error signals that drive synaptic plasticity and refine internal models of the external world. Although evidence supports a key role for Purkinje cells in motor timing adaptation, it remains unclear how they integrate sensory, motor, and reward information to encode temporal expectations and guide adaptive behavior. We addressed this question using active and passive behavioral paradigms in mice. In the active paradigm, animals performed a temporally precise behavior involving two lever pushes that were either self- or externally timed, with the interval between pushes changing unexpectedly within a session to probe prediction errors and adaptation. In the passive paradigm, mice were presented with repeating auditory and visual stimuli, which included unexpected changes in stimulus timing. To investigate the neural basis of temporal expectation, we used two-photon calcium imaging of Purkinje cell dendritic activity during both paradigms. Behavioral analysis of the active task revealed that mice employ a mixed strategy, integrating global contextual knowledge and single-trial outcome information to adapt their motor timing. Neural analysis revealed functionally distinct neuronal subtypes encoding sensory, motor, reward, and prediction signals, which were spatially organized, in alignment with the cerebellar cortex microzonal structure. Both paradigms demonstrated that Purkinje cell dendrites encode temporal expectation signals. Our results shed light on the mechanisms by which the cerebellum can learn the temporal structure of the environment.

Disclosures: S. Aminnaji: None. **J. Zhu:** None. **F. Najafi:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.14/EE4

Topic: F.02. Cerebellum

Support: KAKENHI the Grants-in-Aid for Scientific Research (C) 25K14424

Title: Computational reconstruction of diverse clinical phenotypes in cerebellar motor learning using the tandem learning theory of cerebellar internal models

Authors: *T. HONDA[1,2,3];
[1]Japan Intl. Univ., Ibaraki, Japan; [2]Mita Intl. Sch. of Sci., Tokyo, Japan; [3]Tokyo Metropolitan Univ., Tokyo, Japan

Abstract: Cerebellar motor learning requires the continuous updating of internal models. We previously proposed a tandem learning theory for forward and inverse models to explain fast and slow components of prism adaptation in hand-reaching tasks. Recently, in a multicenter clinical study involving patients with spinocerebellar degeneration, we classified motor learning deficits

into four distinct behavioral phenotypes (Types I to IV) based on specific phases of prism adaptation: acquisition (correct touches during late prism exposure), retention (aftereffects upon initial prism removal), and extinction (readaptation to baseline during late removal). Type I exhibits deficits in both acquisition and retention; Type II shows selective retention deficits; Type III displays isolated extinction deficits. We also discovered a novel Type IV phenotype, characterized by significant baseline reaching errors paradoxically masked during visual shift but immediately returning to baseline upon prism removal. This geometric coincidence indicates a profound failure in internal model recalibration.Here, we explore the computational mechanisms underlying these diverse clinical manifestations. We conducted computer simulations of the prism adaptation task using our tandem learning framework. By modulating the error-sensitivity and updating parameters of the forward and inverse modules, we successfully reproduced the hand-reaching points of four clinical phenotypes. In our simulation, Type I behaviors were explained by the impairment of the forward model, preventing synaptic weight updates. Type II behaviors were replicated by a selective impairment of the inverse model while leaving the forward model intact, mirroring the loss of slow adaptation. Type III behaviors were explained by asymmetry caused by dysfunction of synaptic plasticity in the forward model. Notably, the novel Type IV phenotype was computationally reconstructed by simulating a severe breakdown in error-sensitivity in the forward model, combined with an intrinsic spatial bias in the inverse model. This condition completely abolished new learning and simulated the coincidental geometric masking observed in these patients.Our results suggest that the wide spectrum of clinical phenotypes in patients with cerebellar degeneration can be theoretically explained by specific patterns of impairment in the tandem learning of cerebellar internal models. This validates the tandem learning theory and provides a computational framework to link behavioral symptoms with cerebellar pathophysiology, facilitating the development of model-based digital biomarkers for future therapeutic trials.

Disclosures: T. Honda: None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.15/EE5

Topic: F.02. Cerebellum

Title: Disrupted Cerebellar Timing Control in the Yips: A Hybrid Deep Phenotyping and Liquid State Machine Approach

Authors: *T. AKIHISA[1,2], S. MASUYAMA[1,2], T. HONDA[2,3,1];
[1]MITA Intl. Sch. of Sci., Setagaya, Japan; [2]Japan Intl. Univ., Ibaraki, Japan; [3]Fac. of Humanities and Social Sciences,, Tokyo Metropolitan Univ., Tokyo, Japan

Abstract: The "yips" is a highly context-dependent motor dysfunction characterized by involuntary movements during specific tasks. Recent literature suggests that the yips may

manifest as a form of task-specific dystonia, and cerebellar dysfunction has been implicated during dystonic attacks. Here, we address the hypothesis that the underlying neural mechanism of the yips involves an impairment in the timing control functions of the cerebellum. To test this hypothesis, we adopted a hybrid strategy combining single-subject longitudinal deep phenotyping with advanced computational modeling.First, we conducted longitudinal behavioral tracking of a baseball player experiencing the yips. We recorded 33 consecutive pitches under consistent conditions and extracted quantitative coordinates of the ball position at the exact moment of release using video analysis. Statistical analysis revealed that 20 out of 33 pitches (60.6%) deviated significantly to either the left or right of the target, resulting in uncompleted catches. We computed the mean and standard deviation of these coordinates to rigorously quantify the anomalous intra-subject variance and behavioral instability inherent to the condition.Next, we built a computational model for cerebellar motor control using a Liquid State Machine (LSM) optimized for temporal processing, and analyzed its dynamics. The empirical mean and standard deviation from the 33 pitches served to anchor and validate the baseline state of our computational architecture. Furthermore, we performed simulations by systematically introducing parameter noise into the LSM's temporal processing circuits. Specifically, by mimicking flawed internal clock mechanisms and incomplete long-term depression (LTD) at parallel fiber-Purkinje cell synapses, we observed that the simulation successfully reproduced the precise distribution and variance observed in the empirical yips data.Our results suggest that the yips arise from a pathophysiological state of disrupted cerebellar timing control. This study validates our hypothesis and demonstrates that combining high-resolution longitudinal tracking of a single subject within silico computational modeling can effectively circumvent the noise of heterogeneous group studies. Taken together, it provides a powerful computational template for personalized sports science and precision medicine.

Disclosures: T. Akihisa: None. **S. Masuyama:** None. **T. Honda:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR365.17/EE7

Topic: F.02. Cerebellum

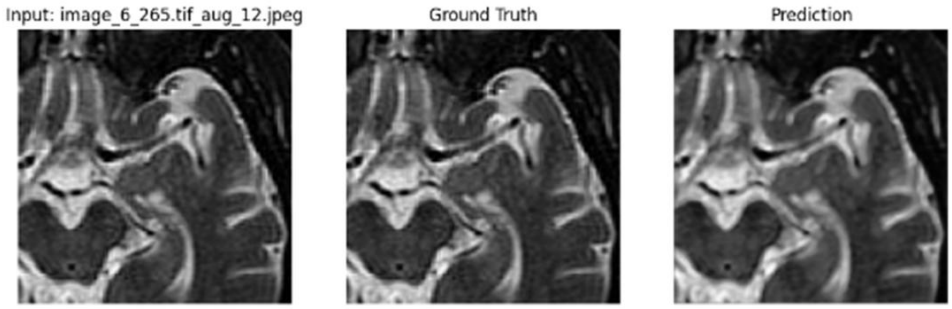
Title: Attention-Enhanced Deep Learning for Midbrain MRI Segmentation in Parkinson’s Disease

Authors: *C. MAHAPATRA[1], A. KAUR[2];
[1]SRMIST Delhi, New Delhi, India; [2]Mol. and cellular biology, Univ. of California, San Francisco, union city, CA

Abstract: Background: Structural alterations in the midbrain are closely associated with neurodegeneration in Parkinson’s disease (PD). Accurate segmentation of the midbrain from magnetic resonance imaging (MRI) is therefore essential for developing quantitative imaging

biomarkers [1]. This study develops an automated deep learning framework for robust midbrain segmentation in MRI data of Parkinson's disease patients. **Methods:** T2-weighted axial MRI scans from the Parkinson's Progression Markers Initiative dataset were used, including **151 PD subjects and 100 healthy controls**. Thirty expert-annotated scans were used for supervised model training. An **Attention-Enhanced U-Net architecture** was implemented, incorporating attention gates within skip connections to improve spatial feature selection. MRI images were preprocessed using center cropping, normalization to the range [−1,1], and resizing to 256×256 pixels. The model was trained using the Adam optimizer and binary cross-entropy loss for up to 50 epochs with early stopping. Performance was evaluated using accuracy, Dice coefficient, F1 score, and mean Intersection-over-Union. **Results:** The proposed model achieved **84.2% segmentation accuracy**, with a **Dice coefficient of 0.82** and **mean IoU of 0.78**, outperforming baseline convolutional neural network models. Visual analysis shows close agreement between predicted segmentation masks and expert annotations, highlighting the model's ability to isolate the midbrain region effectively. Figure 1 shows the **Visual Comparison of Input, Ground Truth, and Predicted Segmentation Conclusion:** Attention-enhanced deep learning enables accurate automated midbrain segmentation and may support the development of MRI-based biomarkers for early detection and monitoring of Parkinson's disease. **References**

1. Mahapatra C., Manchanda R. Computational assessment of calcium channel effects on subthalamic nucleus neuronal cells: abnormal bursting patterns in Parkinson's disease. *Movement Disorders*. 2016.



Disclosures: C. Mahapatra: None. **A. Kaur:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR365.18/EE8

Topic: F.02. Cerebellum

Support: NIH R01 NS072406
NIH R01 DC004154
NIH R01 EY031972

Title: Pharmacological reset of cerebellar plasticity restores learning in a mouse model of Fragile X syndrome

Authors: *A. M. SHAKHAWAT[1], J. L. RAYMOND[2];
[2]Neurobio., [1]Stanford Univ., Stanford, CA

Abstract: In the *Fmr1* knockout (KO) mouse model of Fragile X Syndrome, enhanced long-term depression (LTD) has been reported at synapses throughout the brain, including cerebellar parallel fiber (PF)-Purkinje cell synapses. Yet *Fmr1* KO mice are impaired on cerebellar learning tasks that are known to depend on PF-Purkinje cell LTD. We hypothesize that this paradox can be explained by metaplasticity: an enhanced propensity for LTD at the synapses of *Fmr1* KO mice may allow spontaneous activity in the circuit to aberrantly recruit LTD and thereby raise the threshold for subsequent LTD induction, reducing the availability of LTD for learning. The metaplasticity conceptual framework points to the period before training as a potential therapeutic window. Accordingly, we previously showed that reducing neural activity with diazepam during a period before training restores learning in Purkinje cell specific *L7-Fmr1* KO mice. Here, we further tested the plasticity-reset strategy by inhibiting or enhancing endocannabinoid signaling, which is essential for PF-Purkinje cell LTD, before or during behavioral training. AM251 is an antagonist of the CB1 cannabinoid receptor, which has been shown to block PF-Purkinje cell LTD. Administration of AM251 just before training profoundly and selectively impaired LTD-dependent forms of oculomotor learning. In contrast, AM251 administered 18-24 hours before training restored LTD-dependent oculomotor learning in *L7-Fmr1* KO mice, without altering LTD-independent learning or enhancing learning in wild-type mice. To enhance endocannabinoid signaling, JZL184, a monoacylglycerol (MAGL) inhibitor was administered. In both wild-type and *L7-Fmr1* KO mice, JZL184 delivered just before training enhanced oculomotor learning. However, if` instead, JZL184 was delivered to WT mice 18-24 hrs before training, this recapitulated the oculomotor learning impairments observed in vehicle-treated *L7-Fmr1* KO mice. Together, these findings support a pharmacological plasticity reset strategy for restoring learning in Fragile X Syndrome. Enhanced LTD may engage metaplasticity mechanisms in a way that raises the threshold for plasticity *in vivo* and reduces learning capacity. Pharmacological manipulation of the recent history of plasticity can reset the plasticity threshold and restore learning.

Disclosures: A.M. Shakhawat: None. **J.L. Raymond:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.19/EE9

Topic: F.02. Cerebellum

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R01 NS072406
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Simons Collaboration on the Global Brain 542989

Title: Sensory experience recalibrates the temporal rule for associative synaptic plasticity in the cerebellum

Authors: *H. SHIM[1], J. L. RAYMOND[2];
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Abstract: Learning from delayed feedback requires the brain to assign credit across time, selecting which earlier neural activity to hold responsible for a good or bad outcome. A candidate solution to this temporal credit assignment problem is through the timing rules for synaptic plasticity. A set of synapses in the oculomotor cerebellum offers a tractable test. During oculomotor learning, the association between parallel fiber (PF) and climbing fiber (CF) activation—conveying sensory input driving the behavior and visual feedback about errors, respectively—determines changes in synaptic weights at PF-Purkinje cell synapses. Long-term depression (LTD) at PF-Purkinje cell synapses is recruited only when PF precedes CF input by ~120 ms in slice recordings, matching the delay of visual CF feedback about errors during oculomotor learning *in vivo*. We assessed the extent to which this highly specialized timing rule for plasticity is hardwired versus shaped by experience.We found that the 120-ms timing requirement for LTD is not fixed but is altered by experience: adult dark-rearing, which removes the visual feedback about oculomotor errors, shifts the LTD-inducing interval to short PF-CF delays. Midway through the transition between plasticity rules, LTD was induced by PF-CF pairing intervals intermediate between the normal effective interval of 120 ms, and the coincidence-based rule observed after ~60 days in darkness, indicating that the eligibility window for LTD shifts gradually from ~120 ms toward 0 ms, sliding progressively rather than switching between two discrete states. To further assess the extent to which experience can alter the timing rules for plasticity, we reared mice under dimmed luminance, which delays the visual feedback about errors rather than removing it. After weeks of this altered experience, the timing rule for PF-Purkinje LTD was distinct from those of both normal and adult dark-reared mice, suggesting that different feedback environments generate different timing rules rather than selecting among fixed alternatives.These findings support the hypothesis that the timing rule for cerebellar plasticity is continuously recalibrated by experience, matching synaptic credit assignment to the timing statistics of neural feedback about behavioral errors. This experience-driven temporal metaplasticity of cerebellar synapses could support the temporal accuracy of learning.

Disclosures: H. Shim: None. **J.L. Raymond:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR365.20/EE10

Topic: F.02. Cerebellum

Support: NIH Grant NS112312

Title: Cerebellar plasticity controls seconds-long adaptive brain-wide internal timing

Authors: *R. GAO[1], J. ZHU[2], W. ZHONG[1], C. WANG[1], H. KAKU[1], L. D. LIU[2], A. THOMAS[2], N. LI[1];
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Abstract: The ability to flexibly adjust the cadence of actions and internal processes is fundamental to behavior, from self-paced movements to decision-making and planning. Although internal speed control is reflected in neural activity across distributed forebrain circuits, the mechanisms that enable flexible control of seconds-long neural dynamics remain unclear. Here we show that adaptive control of brain-wide internal timing critically depends on plasticity in the cerebellum, specifically in Purkinje cells. Using task manipulations, large-scale recordings, and targeted perturbations in mice, we found that action planning in frontal cortex is governed by an internal timer that anticipates task timing and flexibly scales the speed of neural trajectories over seconds. Strikingly, selectively blocking Purkinje cell plasticity with a genetically encoded, light-inducible CaMKII inhibitor froze behavior at its previously learned timing and prevented adaptation of action planning dynamics to new task demands. These internally timed dynamics unfolded simultaneously in frontal cortex and its reciprocally connected thalamus, yet their progression was robust to transient disruption of thalamo-cortical activity. In contrast, their progression selectively depended on cerebellar input to thalamus. Together, these findings identify the cerebellum as an essential controller of seconds-long internal neural computation, extending its role beyond rapid motor coordination to a learned controller of brain-wide neural dynamics.

Disclosures: R. Gao: None. **J. Zhu:** None. **W. Zhong:** None. **C. Wang:** None. **H. Kaku:** None. **L.D. Liu:** None. **A. Thomas:** None. **N. Li:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.21/EE11

Topic: F.02. Cerebellum

Support: NIH Grant R15CA271450

Title: Cognitive outcomes after developmental cerebellar injury reflect interconnected cognitive networks

Authors: *R. F. TEGIACCHI[1], E. J. MALLOY[2], K. M. COOK[3], K. S. WALSH[4], C. J. STOODLEY[3];
[1]Neurosci., [2]Mathematics and Statistics, American Univ., Washington, DC; [3]Developing Brain Inst., [4]Pediatric Neuropsychology, Children's Natl. Med. Ctr., Washington, DC

Abstract: There is an increasing appreciation of the role of the cerebellum in cognition and cognitive development, and the cerebellum is thought to modulate the cortical networks that are crucial to typical cognitive functioning. Specific cerebellar subregions have been shown to support language, executive functioning, and emotional processing. We hypothesized that developmental cerebellar injury would have an impact on sensorimotor and cognitive functions - and associated networks - depending on the topography of the injury within the cerebellum. We conducted lesion-symptom mapping in n=61 patients with a history of cerebellar tumor (40M, 21F; age at MRI M±SD=11.99±4.40, average at neuropsychological evaluation M±SD=9.52±3.80) using clinical T1-weighted MRI scans. To assess the networks potentially impacted by interrupted communication between the cerebellum and the cortex, we used each patient lesion map as a seed and extracted the functional networks typically associated with that seed. We then calculated the percent overlap (Dice coefficient) between the lesion-based networks and 7 functional networks (Yeo et al. 2011). We first used t-tests first to compare patients with clinical cerebellar syndromes (Cerebellar Motor Syndrome [CMS], Posterior Fossa Syndrome [PFS], Cerebellar Cognitive Affective Syndrome [CCAS]) to patients without each diagnosis. Second, we performed regression analyses to see if the overlap between the lesion-associated network and specific cortical networks predicted behavioral scores. Preliminary results showed no significant differences for patients with CMS or CCAS. Patients diagnosed with PFS (21%) had lower performance on multiple cognitive tasks including verbal comprehension (p=0.032), semantic fluency (p=0.047), and working memory (p=0.014) and these lesions had significantly lower cortical network overlap in the frontoparietal network (p=0.039), such that networks associated with PFS diagnosis deviated significantly more from the typical networks. Lesion-network overlap with the frontoparietal network significantly predicted working memory scores (p=0.007). Overlap between the default mode network (DMN) and lesion-associated networks was significantly predictive of processing speed (p=0.007) and the parent report of social problems (p=0.003). These findings indicate that cognitive outcomes after developmental cerebellar lesions are associated with altered connectivity with the frontoparietal cognitive control network. Future work will use voxel-based morphometry to evaluate grey and white matter differences in these networks based on lesion location within the cerebellum.

Disclosures: R.F. Tegiacchi: None. **E.J. Malloy:** None. **K.M. Cook:** None. **K.S. Walsh:** None. **C.J. Stoodley:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR365.22/EE12

Topic: F.02. Cerebellum

Title: Computational modeling of emotion via cerebellar tandem learning theory: A dual-process mechanism for fear extinction and context renewal

Authors: *S. MASUYAMA[1,2], T. HONDA[2,1,3];
[1]Mita Intl. Sch. of Sci. High Sch., Setagaya-ku, Japan; [2]Japan Intl. Univ., Ibaraki, Japan; [3]Tokyo Metropolitan Univ., Tokyo, Japan

Abstract: Clinical findings of the cerebellar cognitive-affective syndrome (CCAS) highlight the cerebellum's involvement in emotion. We previously proposed the tandem learning theory (TLT) of forward and inverse models to explain cerebellar motor learning. Here, we extend TLT to emotional regulation and fear conditioning. To bridge cerebellar computation and emotion, we developed a TLT emotion model mapping context-dependent conscious “feelings” (associated with the prefrontal cortex-cerebellar network) to a forward model and context-independent unconscious “affect” (associated with the amygdala-cerebellar network) to an inverse model.Using numerical simulations with two interacting state variables, we compared the model with the Rescorla-Wagner model (RWM). Under a single-state updating formulation, RWM tended to overwrite prior associations during extinction. In contrast, the dual-process architecture of TLT naturally accounts for renewal and spontaneous recovery, reproducing fear resurgence after context shifts without explicitly incorporating latent-cause inference mechanisms.We propose a two-layered dynamic cancellation structure with distinct learning timescales. In this framework, extinction learning is not complete memory erasure but dynamic suppression: the fast-adapting context-dependent forward model (cognitive brake) learns a negative value in a specific context and suppresses the output of the slow-updating context-independent inverse model (emotional core). Simulations further showed that, in a novel context, the forward model rapidly attenuates because of absent contextual reinforcement, releasing inhibition and unmasking preserved unconscious fear in the inverse model.The model also predicted that impairments within the tandem structure produce distinct emotional-disorder phenotypes. Pathologies lacking the corrective transfer mechanism from the forward to the inverse model were associated with persistent fear-like states, replicating the emotional dysmetria observed in CCAS. The model’s premise that the cerebellar forward model regulates fear through prediction-error computation aligns with a recent human study (Batsikadze et al., 2026) showing that non-invasive cerebellar stimulation during extinction prevents spontaneous fear recovery.These findings suggest that replacing single-variable plasticity with the interaction of two variables operating at different timescales provides computational advantages. The results support TLT as a biologically plausible framework for emotional recurrence and offer new insights into emotional learning and trauma.

Disclosures: S. Masuyama: None. **T. Honda:** None.

Poster

PSTR365: Cerebellum: Sensorimotor, Behavior, and Learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR365.23/EE13

Topic: F.02. Cerebellum

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Title: Nonlinear mixed selectivity in cerebellar inputs facilitates context-dependent learning

Authors: *X. CHEN[1], J. F. MEDINA[2];
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Abstract: To support flexible behavior, the brain must represent the same input differently across contexts. Nonlinear mixed selectivity offers an attractive solution by combining sensory and contextual signals into representations that allow different behavioral responses to be learned for the same stimulus. Yet whether nonlinear mixed selectivity causally facilitates this context-dependent learning remains unknown. Here we investigated the origin and functional consequences of nonlinear mixed selectivity in the cerebellum, where granule cells have traditionally been thought to generate context-dependent representations by combining mossy fiber inputs. Using Neuropixels probes, we recorded the activity of mossy fiber populations as the same visual stimulus was delivered in two different behavioral states: rest and locomotion. We found that sensory and state signals were nonlinearly mixed within the mossy fiber inputs themselves, before granule cell processing. Locomotion profoundly reconfigured mossy fiber responses rather than simply scaling them, thereby increasing the separability of population representations across states. To test whether this reconfiguration causally facilitates context-dependent learning, we used a cerebellar task in which mice learned to respond to the visual stimulus in one state but not the other. Mice successfully learned this discrimination, whereas replacing the visual stimulus with optogenetic mossy fiber stimulation reduced state-dependent reconfiguration and impaired learning. These findings establish nonlinear mixed selectivity in cerebellar input pathways as a causal mechanism for context-dependent learning and behavioral flexibility.

Disclosures: X. Chen: None. **J.F. Medina:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

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Program #/Poster #: PSTR366.01/EE14

Topic: F.07. Rhythmic Pattern Generation

Support: NIH Grant R01NS121220

Title: Connecting population activity trajectories to the underlying locomotion network in Aplysia with synthetic motor programs

Authors: *D. S. KOVALEV[1], W. N. FROST[2];
[1]Stanson Toshok Ctr. for Brain Function and Repair, [2]Chicago Med. Sch., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Dimensionality reduction (e.g., PCA) is widely used to construct low-dimensional trajectories to find generalities needed to interpret heterogeneous neural network activity. However, network property implications of geometric features of trajectories are often uncertain. In *Aplysia californica*, the CPG-driven efferent pedal ganglion network driving gallop-crawl escape motor program (MP) arises from a low-dimensional spiral attractor, where each orbit corresponds to one locomotor cycle (Bruno et al., 2017). However, it remains unclear how specific changes in the underlying network features are reflected in the spiral attractor. We approached this question by developing a MATLAB-based generator of synthetic MPs with controlled network properties such as intraburst spiking rates, burst phase shifts, and neuronal recruitment. PCA analysis of synthetic datasets revealed distinct trajectory signatures associated with specific network features. Increasing the intraburst spiking rate widened the trajectory diameter, but did not shift the centroid location. Recruitment of neurons during ongoing activity increased the trajectory diameter, and when recruitment involved half of the population, it produced centroid shifts. Subsequently, we applied this framework to voltage-sensitive dye recordings of spiking activity of more than 100 real neurons in *Aplysia* isolated brain preparations during tail nerve-induced locomotor MPs. To determine contributions of specific network components, we constructed PCA trajectories from selected network subpopulations. Thus, we extracted the building blocks of the motor network to reveal the influence of distinct functional groups on trajectory geometry. Trajectory changes predicted by the synthetic MPs were recapitulated in the real biological network. We observed the same trajectory diameter changes and centroid shift associated with the neuronal recruitment. These findings contribute to a framework for decoding low dimensional population activity trajectories by linking specific geometric features to the underlying network features in *Aplysia* motor network. These results motivate further efforts to use synthetic locomotion MPs to understand how other network properties impact geometry of low-dimensional trajectories in *Aplysia* and other preparations amenable to large scale recording of networks.

Disclosures: D.S. Kovalev: None. **W.N. Frost:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

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Program #/Poster #: PSTR366.02/EE15

Topic: F.07. Rhythmic Pattern Generation

Support: R35NS142987

Title: Spatial cable modeling of robust rhythmic output in stomatogastric circuits

Authors: *S. RAUTU[1], E. E. MARDER[2];
[1]Brandeis Univ., Waltham, MA; [2]Biol., Brandeis Univ., WALTHAM, MA

Abstract: Small rhythmic circuits such as the lobster stomatogastric ganglion generate stable motor patterns despite variability in neuronal morphology, membrane conductances, synaptic strength, and electrical coupling. In lobsters, pyloric rhythms are also maintained from juvenile to adult animals despite substantial growth of the animal, ganglion, and constituent neurons. These observations raise a spatial question: how do ion-channel placement, synaptic location, electrical coupling, and neuronal geometry shape excitability and circuit timing in extended neuronal arbors?
To address this problem, we developed a spatially extended conductance-based model of branched neurons and small circuits. Rather than reducing neurites to chains of locally isopotential compartments, the method numerically solves the active cable equation on continuous branches, retaining spatial voltage variation and axial current flow. We implemented this with a sparse high-order spectral solver, allowing accurate and efficient computation of spatial voltage profiles and axial currents while voltage-gated, calcium-dependent, and synaptic conductances are assigned to prescribed locations along the branches. Branch points enforce voltage continuity and axial-current conservation, and distinct neurons can be coupled through localized chemical synapses or gap-junctional electrical synapses.
Using this framework, we constructed STG-like branched neurons and small circuits in which morphology, conductance density, channel localization, synaptic placement, and coupling strength can be varied independently. This provides a computational setting for examining how spatial organization within neurons shapes signal propagation, spike initiation, and circuit-level rhythmic output across different neuronal geometries.

Disclosures: S. Rautu: None. **E.E. Marder:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

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Program #/Poster #: PSTR366.03/EE16

Topic: F.07. Rhythmic Pattern Generation

Title: Central versus peripheral neural control of a coordinated walking pattern in Drosophila.

Authors: *N. SAPKAL[1,2], N. MANCINI[3], S. S. BIDAYE[4];
[1]Florida Atlantic Univ., JUPITER, FL; [2]Max Planck Florida Inst. for neuroscience, Jupiter, FL; [3]Max Planck Florida Inst. for Neurosci., Jupiter, FL; [4]Max Planck Florida Inst. For Neurosci., Jupiter, FL

Abstract: The nature and role of central pattern generators (CPGs) in walking have been debated for over a century. While various models, ranging from half-center oscillators to large-scale neural population dynamics, have been proposed, a complete wiring diagram of a locomotor

CPG remains elusive. Furthermore, the relative contributions of central rhythm-generating circuits and sensory feedback from stepping legs to walking behavior remain unclear. Using a genetically targetable set of walking-promoting neuronal populations that drive stepping in specific leg domains, we dissect the contributions of central and peripheral inputs to locomotor pattern generation in the fruit fly. To separate these contributions, we developed a novel sensory-deprivation paradigm that reveals locomotor dynamics normally masked by proprioceptive feedback. Under these conditions, we provide evidence that each leg is governed by its own CPG module with an inherent cycle period. We further show that load-dependent sensory signals generated by substrate contact, together with descending brain commands, sculpt the temporal structure of individual step cycles. We demonstrate that central coupling mechanisms underlie both within-segment (left-right) and across-segment (front-middle-hind) interleg coordination, while proprioceptive feedback and descending commands flexibly tune this coupling in a task-specific manner. We identify co-activation of specific descending neurons as a mechanism for accelerating locomotor rhythms. Finally, by constraining connectome-based circuit searches with our experimental findings, we identify candidate neural circuit motifs that may underlie the generation of coordinated six-legged walking.

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Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

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Topic: F.07. Rhythmic Pattern Generation

Support: DFG, German Research Foundation - 233886668/ GRK1960

Title: Analysis of lateral network connectivity and rhythmic membrane potential modulations in an insect sensorimotor network

Authors: *A. RUTHE[1], C. GEBEHART[2,1], M. HAUSTEIN[1], A. BUSCHGES[1];
[1]Univ. of Cologne, Cologne, Germany; [2]Neurosci., Champalimaud Res., Lisbon, Portugal

Abstract: The motor activity for terrestrial locomotion, such as walking, emerges from the actions of neuronal networks that transform descending, ascending, local sensory and central signals into a task-specific motor output. Within the insects' nervous system, premotor nonspiking interneurons (NSIs) are integral parts of sensorimotor pathways, and ample information is available on their role in posture control and locomotion. However, the influence of lateral interactions among these pathways, i.e., specifically between NSIs, which are known to exist, has received only sparse attention up to now (Gebehart and Büschges 2021; Burrows 1996). To shed light on this issue, we examined interactions among NSIs in the premotor network that controls movement of the stick insects' middle leg. To this end, neuronal activity was assessed using single and paired sharp electrode intracellular recordings at rest, during

stimulation of load (campaniform sensilla) and movement sensors (femoral chordotonal organ), and after pharmacologically blocking synaptic transmission. Current injections into pairs of simultaneously recorded NSIs uncovered lateral connections, such as reciprocal excitation between NSIs. Moreover, further analysis of individual NSI recordings revealed low-amplitude rhythmic modulations of their membrane potential that were restricted to a subset of neurons, occurring in only six of eleven identified NSI types. Interestingly, these modulations were consistently observed, across recordings and neuron types, at a frequency of approximately 30 Hz. Findings from current injections and synaptic blockers suggest that these modulations arise from network interactions, such as synaptic inputs. Given that these rhythmic modulations were observed only in a subset of NSIs, it is unlikely that they represent a uniform network feature, but instead may reflect functional segregation within the network. Our ongoing work aims to determine whether these rhythmic membrane potential modulations shape the processing of incoming synaptic inputs, such as those from sensory afferents. In addition, we are investigating whether these rhythmic modulations are state-dependent and altered during motor activities, such as forward and backward stepping of the leg. By characterizing the interactions between NSIs, this work will contribute to a more comprehensive understanding of how distributed sensorimotor networks contribute to motor control.

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Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

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Topic: F.07. Rhythmic Pattern Generation

Support: NIH Grant NS134170
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Title: Functional Dissection of Distinct Populations of Glutamatergic Spinal Neurons in Locomotion

Authors: A. COLEMAN, *M. A. MASINO;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Spinal locomotor networks have the intrinsic capacity to convert unorganized excitatory drive into organized locomotor output, even in the absence of sensory input and higher-order input from the brain. Although many features of spinal locomotor pattern-generating networks, such as their ventral location, neuronal composition, and activation by glutamatergic excitation, are shared among vertebrates, an understanding of the functional roles of distinct populations of spinal glutamatergic neurons (e.g., V0v, V2a, and V3) that compose these circuits is incomplete. To determine the sufficiency of each glutamatergic spinal neuron population to produce locomotor activity, the effects of optogenetic activation on locomotor

output in spinalized transgenic larvae expressing channelrhodopsin-2 in spinal glutamatergic neurons was measured with high-speed videography (180 frames/s). Photostimulation was sufficient to evoke episodically-organized locomotion in both V0v (*evx1:Gal4:UAS:ChR2*; 8 of 15 (53%)) and V2a (*vsx2:Gal4:UAS:ChR2*; 7 of 10 (70%)) larvae, but had limited sufficiency in V3 (*nxk2.2ab:Cre-mCherry-NLS; vglut2a:loxP-DsRed-loxP-ChR-GFP*; 1 of 5 (20%)) larvae. V2a photostimulation generated significantly more episodes (two-way ANOVA, $p<0.001$, $n = 7$) compared to V0v photostimulation, while V0v photostimulation produced a significant increase in tail-bend frequency (two-way ANOVA, $p<0.001$, $n = 8$) and amplitude (two-way ANOVA, $p<0.05$, $n = 8$) compared to V2a photostimulation. There were no significant differences in other locomotor measures. Next, to measure the effects of optogenetic activation of distinct populations of spinal glutamatergic neurons on the properties of NMDA-induced locomotion, high-speed videography (180 frame/s) was combined with photostimulation in spinalized transgenic larvae expressing channelrhodopsin-2 in spinal glutamatergic neurons. V0v photostimulation increased episode duration (614%), tail-bend frequency (9%), and tail-bend amplitude (79%). V2a photostimulation increased episode duration (2886%), tail-bend frequency (44%), and tail-bend amplitude (220%). V3 photostimulation increased episode duration (180%) and tail-bend amplitude (53%). These outcomes demonstrate that the V0v and V2a, but not V3, spinal neuron populations are sufficient to generate locomotion and that all three populations increase episode duration and tail-bend amplitude, while only the V0v and V2a populations increase tail-bend frequency, which provides evidence that distinct glutamatergic spinal neuron populations contribute differentially to the initiation and output of vertebrate locomotion.

Disclosures: A. Coleman: None. **M.A. Masino:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

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Topic: F.07. Rhythmic Pattern Generation

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Title: NMDA-Evoked Spinal Locomotor Activity is Concentration Dependent and Differs Across Development in Zebrafish Larvae

Authors: *L. J. BECK, S. HIGLEY, A. LEWIS, M. A. MASINO;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Spinal locomotor networks have the intrinsic capacity to transform unpatterned excitatory input into patterned output. Locomotion in zebrafish larvae consists of discrete episodes of swimming. Conventionally, locomotor activity in zebrafish larvae is evoked by *N*-methyl-d-aspartate (NMDA) application. Our previous work demonstrated a developmental

difference in locomotor activity between 3 and 4 days post-fertilization (dpf); the proportion of spinalized larvae that produced NMDA-evoked fictive locomotion (e.g., peripheral nerve recordings) was significantly lower ($z = 5.51$; $p < 0.001$) in 3 dpf larvae (35 of 236 (15%)) compared to 4-7 dpf larvae (23 of 45 (51%)). This result suggests that 50 μM NMDA may not be efficient at generating locomotor output in fictive preparations at either developmental stage. Therefore, we performed a concentration-response paradigm to identify NMDA concentrations that produced robust and stable locomotor output in 3 and 4-6 dpf larvae. High-speed videography (60 frames/s) to record (60 min) and measure behavioral locomotor output (6 x 10 min time windows) in spinalized larvae in response to different NMDA concentrations (50 (lo) or 100 (hi) μM). All values below are reported as mean (SD). In response to either NMDA concentration applied to 3 dpf larvae, the number of episodes increased from the 1st (lo = 1.0 (1.6); hi = 1.9 (3.3)) to the 4th (lo = 145.3 (93.5); hi = 184 (135.7)) time window. In response to 50 μM NMDA, the number of episodes decreased from the 5th (167.5 (99.1)) to the 6th (92.0 (65.4)) time window, while the number of episodes remained relatively stable during 100 μM NMDA application from the 5th (150.9 (164.3)) to the 6th (153.4 (155.8)) time window. The duration of episodes initially increased from the 1st (lo = 0.79 s (0.4); hi = 0.39 s (0.2)) to the 2nd (lo = 1.14 s (0.5); hi = 0.76 s (0.2)) time window. Episode duration decreased from the 3rd (lo = 1.1 s (0.5); hi = 0.76 s (0.2)) to the 6th (lo = 0.35 s (0.1); hi = 0.40 s (0.1)) time window. In response to either NMDA concentration applied to 4-6 dpf larvae, the number of episodes increased from the 1st (lo = 0; hi = 6.3 (13.5)) to the 4th (lo = 218.8 (128.8); hi = 327.6 (128.8)) time window, and became stable from the 5th (lo = 265.9 (97.9); hi = 328.6 (116.5)) to the 6th (lo = 269.9 (121.4); hi = 327.1 (103.4)) time window. The duration of episodes increased from 1st (lo = 0 s; hi = 0.43 s (0.1)) to the 6th (lo = 0.66 s (0.8); hi = 0.97 s (0.5)) time window. In summary, locomotor output in 3 dpf larvae can be tuned to generate either fewer number of episodes with longer durations (50 μM) or greater number of episodes with shorter durations (100 μM). However, this relationship does not hold for 4-6 dpf larvae.

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Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

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Title: Spatial reconfiguration of commissural inhibition drives swimming mode transitions

Authors: *P. FONTANEL[1], A. PAZZAGLIA[2], A. FERRARIO[2], M. BERTUZZI[1], V. SABHARWAL[1], D. MADRID-PULGARIN[1], L. D. PICTON[1], A. J. IJSPEERT[2], A. EL MANIRA[1];
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Abstract: Locomotion is an embodied behavior, arising from interactions between neural circuits, the body, and the environment. As speed increases, animals must overcome rapidly escalating external forces that cannot be met by simply accelerating a baseline motor rhythm. In terrestrial quadrupeds, this is reflected in discrete gait transitions, from walking to trotting to galloping, to meet the physical demands of movement at a given speed. How spinal circuits dynamically reorganize their output to accommodate these changing biomechanical demands remains a fundamental unresolved question. Here, we address these questions through a combination of behavioral analysis, biomechanical modeling, and circuit physiology in adult zebrafish. We show that increasing swimming speed is accompanied by a discrete locomotor transition from localized tail-driven propulsion to coordinated whole-body undulation, both biomechanically optimal at their respective speeds. Using calcium imaging, optogenetics, and electrophysiology, we examined two commissural inhibitory populations, V0d and dI6, known to be involved in locomotion and left-right alternation, and find that they are organized into distinct spatial coordination systems. V0d interneurons are engaged at slow speeds and maintain recruitment during acceleration, providing long-range descending inhibition, whereas dI6 interneurons are selectively gated during fast swimming to provide local, segmental inhibitory control. Targeted ablations reveal complementary behavioral deficits, demonstrating that each population is required for a distinct locomotor regime. Implementing these empirical architectures back into the biomechanical model recapitulates the locomotor transition and shows that long-range inhibition is efficient at low speed while the addition of local inhibition is required to pattern whole-body engagement at high speed. Together, our findings reveal how spinal inhibitory architecture redistributes commissural inhibition across the body axis to accommodate the changing biomechanical demands of movement, converting continuous excitatory drive into discrete locomotor modes.

Disclosures: P. Fontanel: None. **A. Pazzaglia:** None. **A. Ferrario:** None. **M. Bertuzzi:** None. **V. Sabharwal:** None. **D. Madrid-Pulgarin:** None. **L.D. Picton:** None. **A.J. Ijspeert:** None. **A. El Manira:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.08/EE21

Topic: F.07. Rhythmic Pattern Generation

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Svenska Sällskapet för Medicinsk Forskning (SSMF, S21-0005)
the Swedish Research Council (2022-01453)
Erling-Perssons Stiftelse (2024-0059)

Title: A spinal circuit for social behavior

Authors: *D. MADRID-PULGARIN[1], L. D. PICTON[2], A. PAZZAGLIA[3], Y. WANG[4], M. BERTUZZI[2], A. FERRARIO[5], A. ANASTASIADIS[6], J. ARREGUIT[7], P. FONTANEL[2], C.-X. HUANG[9], K. MULLENERS[8], J. SONG[9], A. J. IJSPEERT[5], A. EL MANIRA[2];
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Abstract: Social behaviors in the animal kingdom are widely attributed to high-order cognitive processing in the brain. However, the effective collective coordination observed in some animal groups, such as fish schooling, can seemingly emerge from rapid, local interactions with environmental cues, suggesting the existence of real-time mechanisms of coordination that bypass higher-order computation. Here, using a combination of calcium imaging, electrophysiology, optogenetics, behavioral analysis, modelling and robotics, we show that a low-order, decentralized spinal sensorimotor circuit is both necessary and sufficient for real-time social coordination during schooling in zebrafish. Central to this circuit are intraspinal proprioceptors, which are specialized mechanosensitive glycinergic neurons located along the ventrolateral edges of the spinal cord. During normal swimming, these neurons detect local body bending (egocentric signals) and deliver direct, curvature-based phasic inhibition to the rhythm-generating V2a interneurons to pace individual locomotion on a cycle-by-cycle basis. Moreover, this same circuit can integrate dynamic environmental perturbations (allocentric signals), such as the neighbor-generated wake vortices encountered during schooling, providing a mechanism for real-time vortex phase matching. To test the sufficiency of this sensorimotor circuit, we developed a biologically faithful spiking neuromechanical model and a bio-inspired robot. Both the model and the robot successfully replicated vortex phase matching. This demonstrates that proprioception alone equips the network with the ability to exploit local hydrodynamic perturbations from conspecifics, yielding significant energetic benefits. Finally, to confirm the necessity of this pathway, we disrupted the circuit using a loss-of-function mutation in the mechanosensitive ion channel *Piezo2*. Disrupting this specific proprioceptive feedback abolished vortex phase matching and severely impaired behavioral coupling between individuals, compromising global schooling. Together, these results demonstrate that a simple, low-order spinal circuit can dynamically orchestrate the real-time synchronization of individuals within a collective, providing a biological mechanism for the emergence of coordinated social behavior.

Disclosures: D. Madrid-Pulgarin: None. **L.D. Picton:** None. **A. Pazzaglia:** None. **Y. wang:** None. **M. Bertuzzi:** None. **A. Ferrario:** None. **A. Anastasiadis:** None. **J. Arreguit:** None. **P.**

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Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.09/EE22

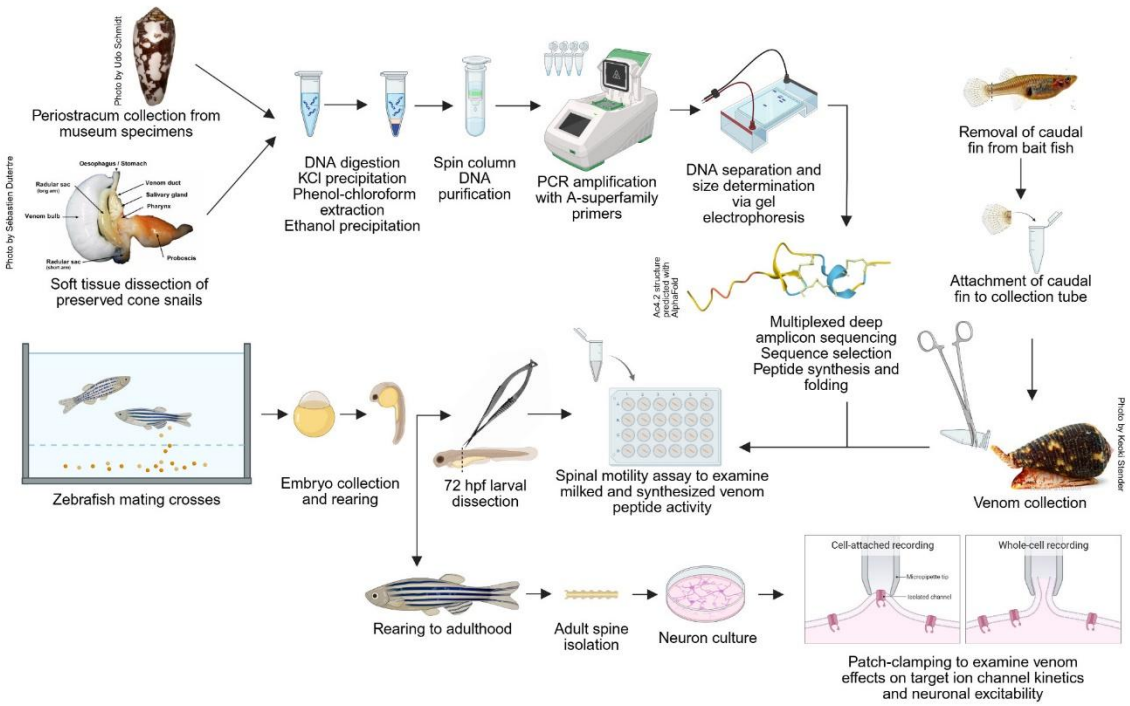
Topic: F.07. Rhythmic Pattern Generation

Support: Kenneth T. Norris Foundation

Title: Identifying Cellular Targets of Cone Snail Peptide Neurotoxins on the Zebrafish Model System

Authors: *K. G. SHEN;
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Abstract: The active components of cone snail venoms are highly modified peptide neurotoxins that have become powerful tools for neuroscience and sources of novel therapeutics, including the FDA-approved drug Prialt(™). Fish-hunting cone snails like Conus catus use a rapid injection system and fast-acting neurotoxins to quickly incapacitate prey. Although these peptides are known to produce rapid paralysis, the molecular targets of the neuroexcitatory (NEX) peptides remain unresolved. To investigate NEX peptide activity, our laboratory developed a zebrafish model system that enables analysis of individual adult spinal neurons in vitro and within intact spinal motor circuits. In addition, our spinal motility assay quantifies circuit-level responses in real time using small-volume parallel assays, motion-tracking software, and spinalized preparations that eliminate supraspinal inputs. Using motility assays, primary cell culture, and patch-clamp electrophysiology in fluorescent transgenic zebrafish lines, we identified the cellular target of NEX peptides and characterized their effects on spinal motor circuits. Cellular targets are confirmed through recordings from fluorescently labeled neurons. We have also observed that NEX peptides induce rapid bodily flexions in the spinal motility assay, and this activity is distinct from coordinated swimming induced by NMDA. Together, these approaches provide quantitative in situ measurements and confirmation of the cell types involved in spinal circuit responses, establishing a foundation for further physiological studies and the development of cone snail venom-derived therapeutics.



Disclosures: K.G. Shen: None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

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Topic: F.07. Rhythmic Pattern Generation

Support: NSERC Discovery Grant RGPIN-2021-03866
Canadian Foundation for Innovation JELF 43065

Title: Mapping Long-Range Spinal V2a Connectivity and Probing Its Behavioral Role with Spinal Cord-Specific Genetic Ablation in Larval Zebrafish

Authors: *Z. LUO[1,2], M. KOYAMA[1,2];
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Abstract: Animals produce complex movements by activating muscles in precise temporal and spatial patterns along the body axis. Spinal V2a interneurons are widely implicated in driving motor output during locomotion. While previous work in adult and larval zebrafish has

characterized their synaptic connections with paired whole-cell recording, these efforts have been largely confined to nearby partners and have not addressed long-range connectivity along the spinal cord, leaving their contribution to coordinated movement across the body axis unclear. To address this, we combined single-cell precision optogenetic stimulation of spinal V2a neurons with whole-cell recordings from axial motoneurons in larval zebrafish, aiming to uncover the long-range connections more systematically and to test whether they could coordinate axial muscle activation along the rostrocaudal axis. Our findings confirm a parallel circuit organization between spinal V2a neurons and motoneurons, mirroring observations in adults, and reveal that both fast and slow modules exhibit potent long-range synaptic connections in addition to local electrical coupling—supporting a role for V2a neurons in the coordinated recruitment of axial muscles during locomotion. To assess the behavioral significance of this long-range connectivity, we established a spinal cord-specific genetic ablation approach based on Diphtheria Toxin A-chain (DTA), restricted to the spinal cord using a Cre line and expressed from the endogenous *vsx2* locus active in differentiating V2a neurons. Following ablation of spinal V2a neurons, animals continued to produce escape and spontaneous swimming, but with significant reductions not only in bend amplitude and frequency but also in the speed at which body bends propagated along the rostrocaudal axis, demonstrating that this cell type shapes the spatiotemporal coordination of axial muscle activity. Together, this work links the synaptic architecture of spinal V2a circuits to their behavioral function, shedding light on the networks facilitating coordinated locomotion in vertebrates.

Disclosures: Z. Luo: None. **M. Koyama:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

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Program #/Poster #: PSTR366.11/EE24

Topic: F.07. Rhythmic Pattern Generation

Support: Swedish Research Council
Knut and Alice Wallenberg Foundation
Brain Foundation
European Research Council

Title: Chx10^{+} brainstem neurons encode the progression of locomotor sequences in adult zebrafish

Authors: *L. MROWKA, V. SABHARWAL, D. MADRID-PULGARIN, M. BERTUZZI, A. EL MANIRA;
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Abstract: Locomotion plays a fundamental role in many aspects of life. Studies in many model systems have unravelled the intricate organization and function of the spinal circuits controlling

locomotor movements. The activity of these circuits is driven by descending neurons from the brainstem. While it is well established that brainstem neurons initiate locomotor activity, whether they encode the temporal sequence of the locomotor cycle remains unclear. Here, we investigate the role of $Chx10^+$ brainstem neurons in adult zebrafish to map the spatiotemporal dynamics of locomotor control. Optogenetic stimulation of $Chx10^+$ neurons across the brainstem revealed that swim activation is strongest in the caudal medulla, coinciding with the largest fraction of $Chx10^+$ descending neurons projecting to the spinal cord. Using *in-vivo* calcium imaging, we identified a subset of medulla $Chx10^+$ neurons that act as an initiator hub that subsequently recruits more $Chx10^+$ neurons caudally. These caudal medulla $Chx10^+$ neurons are activated in a temporal sequence during swimming. This sequential activity pattern was confirmed by whole-cell patch-clamp recordings, revealing that $Chx10^+$ neurons are phase-locked to specific portions of the swim cycle. Consequently, the population ipsilateral to the active muscle contraction encodes the entire "on-cycle" phase of the locomotor burst. Ablation of medulla $Chx10^+$ neurons reduced the number of spontaneous swim cycles, supporting their role in sustaining locomotor progression. We recapitulated this phenotype in an *ex-vivo* preparation by ablating either the $Chx10^+$ initiator hub neurons or a larger number of the caudal population, suggesting that initiator hub neurons are required to recruit the caudal population. Because of their necessity and ability to encode locomotor progression, this caudal population is an amplifier ensemble. Finally, single-cell RNA-seq analysis revealed distinct molecular signatures separating the $Chx10^+$ medulla initiator and amplifier subpopulations. Together, our results provide a novel dual-population model wherein $Chx10^+$ brainstem neurons sustain the duration of a locomotor episode by amplifying descending commands and encoding the precise temporal progression of the swim cycle.

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Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.12/EE25

Topic: F.07. Rhythmic Pattern Generation

Support: Paris Brain Institute DBS

Title: All-optical mapping of the mesencephalic locomotor region in larval zebrafish

Authors: *N. PEYSSON[1,2,3,4], X. JIA[1,2,3,4], P. POUGET[1], K. FIDELIN[1,2,3,4], C. WYART[1,2,3,4]; [1]Paris Brain Inst., Paris, France; [2]INSERM U1127, Paris, France; [3]CNRS UMR 7225, Paris, France; [4]Sorbonne Univ., Paris, France

Abstract: Across multiple vertebrate species, the stimulation of the mesencephalic locomotor region (MLR) elicits forward locomotion. Targeting the MLR therefore represents a promising avenue to recover motor deficits in Parkinson's disease. However, deep brain stimulation of this

region in patients led to inconsistent results, probably reflecting the heterogeneity of neuronal populations intermingled in the MLR. Despite recent progress uncovering MLR functional cell types in rodents, the organization of this region remains difficult to reconcile across species. Here, we combine innovative light patterning and behavior analysis to investigate whether genetically distinct MLR neurons encode different motor actions in the recently identified zebrafish MLR. We unravel the molecular diversity of MLR neurons, constructing a 3D atlas of glutamatergic, cholinergic, and GABAergic neurons combined with multiplexed hybridization chain reaction mapping. Next, we leverage this resource and apply digital holography to spatially restrict the optogenetic activation to small ensembles of genetically defined neurons. Our results demonstrate that the activation of glutamatergic as well as DRD1-expressing MLR neurons elicits forward locomotion. Although motor responses remain highly consistent within individuals across a wide range of optogenetic stimulation frequency and power, responses across individuals vary in terms of tail beat amplitude, duration and locomotor frequency. In contrast, stimulation of glutamatergic neurons expressing *vsx2*$^{+}$ reliably triggers the stereotypical J-turns, a backward movement used during hunting to align the larval zebrafish body with its prey. Altogether, our findings reveal that distinct cell populations in the zebrafish MLR can trigger distinct and specific behavioral responses upon stimulation, ranging from forward swimming to backward orienting behaviors. This feature may reflect the engagement of distinct MLR circuits projecting to the medulla and spinal cord. Together with recent studies in mice reporting diverse outcome (motor initiation, ipsilateral turns) upon MLR stimulation, our observations should help refine stimulation strategies for recovery of motor functions in Parkinson's disease.

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Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

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Topic: F.07. Rhythmic Pattern Generation

Support: Fondation Richard Mille
Agence Nationale de la Recherche (ANR)
European Research Council (ERC)
INSERM
Paris Brain Institute

Title: A molecular atlas of the pedunculopontine and cuneiform nuclei

Authors: *K. FIDELIN[1,2,3,4], M. CARBO-TANO[5], T. TOPILKO[6], M. MEMMADI[1,2,3,4], C. BENEDETTO[1,2,3,4], C. WYART[1,2,3,4];
[1]Paris Brain Inst., Paris, France; [2]INSERM U1127, Paris, France; [3]CNRS UMR 7225, Paris,

France; [4]Sorbonne Univ., Paris, France; [5]Neurosci., Univ. of Copenhagen, Copenhagen, Denmark; [6]Vibraint, Copenhagen, Denmark

Abstract: Electrical and optogenetic stimulation experiments have revealed the nature and location of brainstem motor circuits involved in generating and modulating movement. Among these circuits, the mesencephalic locomotor region (MLR), identified in the caudal mesencephalic reticular formation (MRF), represents one of the most conserved functional regions implicated in generating forward locomotion across vertebrate species. Within this area, cells eliciting locomotion but also cells modulating a larger array of whole-body behaviors have been assigned to either the pedunculopontine (PPN) or cuneiform (CUN) nucleus. However, attempts to find organizational principles based on the location of stimulations, neurotransmitter identity, or projection profiles of stimulated cells have yielded inconsistent results that are difficult to reconcile across species. One reason for this problem lies in the lack of identified marker genes labelling conserved and species-specific neuronal subtypes in both PPN and CUN nuclei. Here, using spatial transcriptomics, we map gene expression and cell type organization of PPN and CUN neurons across the entire caudal mesencephalic reticular formation in the mouse brainstem. Clustering analysis identified major cell types within the MRF, including 10 neuronal clusters spatially confined within PPN and CUN boundaries (6 glutamatergic, 3 GABAergic, and 1 cholinergic). Mapping of clusters *in situ* revealed a previously unappreciated topographic organization of neuronal populations within each nucleus demonstrating that PPN and CUN neurons are not simply intermingled but segregated into distinct three-dimensional domains. Remarkably, our approach identified several marker genes involved in metabolic regulation that define a region previously referred to as the sub-cuneiform nucleus (Sub-CUN), lying at the interface between CUN and PPN. We validated the enrichment of top marker genes using RNAscope *in situ* hybridization and improved the depth of gene sampling by mapping our data to existing spatial transcriptomics and single-cell RNA sequencing datasets. Combined datasets reveal that D1 and D2 receptors are differentially expressed within neuronal clusters, suggesting selective dopaminergic modulation of PPN and CUN subtypes. Finally, we modelled the predictive power of gene expression to determine cell type identity and location within PPN and CUN nuclei. Together, this work reveals a spatial map of neuronal organization within the caudal MRF that will enable MLR cell type targeting for innovative stimulation strategies *in vivo*.

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Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

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Topic: F.07. Rhythmic Pattern Generation

Support: NIH R01-NS125362

Title: Axon tracing of ventral spinocerebellar tract neurons in the intact mouse spinal cord reveals axon collaterals in several spinal segments

Authors: *P. HÖLZER[1], N. DELESTRÉE[1], C. GONG[2], R. TOMER[2], G. Z. MENTIS[1]; [1]Neurol., [2]Biol. Sci., Columbia Univ., New York, NY

Abstract: Locomotion is a fundamental behavior essential for survival in animals. This behavior requires the sequential and coherent activation of various muscles to produce a precise and well-timed movement for each appendage. Key to this process is the central pattern generator (CPG), a spinal interneuron network responsible for generating and maintaining rhythmic and stereotyped motor activity. However, the specific cellular components of this spinal network remain poorly understood. We recently proposed that ventral spinocerebellar tract neurons (VSCTs), a population of spinal neurons residing in the ventral horn and projecting to the cerebellum, constitute an integral component of the CPG. We previously demonstrated that VSCTs are both necessary and sufficient for generating locomotor rhythms in mice. We proposed that VSCTs possess axon collaterals to engage other CPG interneurons and hypothesize that they may play an important role in coordinating spinal segment activity during locomotion. The anatomical characteristics of VSCT neurons are not well known. To address this, we took advantage of recently developed clearing techniques and fast scanning light-sheet microscopy to visualize VSCTs, their axons and their collaterals along the entire mouse spinal cord. Briefly, floxed TdTomato transgenic mice were injected with CAV2-Cre virus in the cerebellum at birth to label spinocerebellar tract neurons. The entire spinal cord was collected at P20, rendered transparent by delipidification and scanned using light-sheet microscopy. We then traced the entire somatodendritic architecture of VSCTs as well as their axons using the Neurolucida 360 software. We found that VSCTs display large cell bodies and form extensive dendritic trees (~1mm). As expected, we found that their axons cross the midline at the spinal segment in which the soma is located and ascend a few segments in the ventral funiculus before turning to the lateral funiculus. Strikingly, we also found a significant portion of VSCTs displaying an ipsilateral axonal projection. Surprisingly, we found that a subset of lumbar VSCTs possess a bifurcating axon projecting both rostrally and caudally. Along their axonal pathway, we identified axon collaterals, their location ranging from the same spinal segment as the VSCT soma to several spinal segments away from it. These findings raise the possibility that VSCTs form extensive neuronal networks which may play an important role in intersegmental connectivity during locomotion.

Disclosures: P. Hölzer: None. **N. Delestrée:** None. **C. Gong:** None. **R. Tomer:** None. **G.Z. Mentis:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.15/EE28

Topic: F.07. Rhythmic Pattern Generation

Support: NIH R01 NS130799

Title: Electrophysiological Signatures of Rhythmic Adult Spinal Shox2 Interneurons Involved in Locomotor Rhythm Generation

Authors: *D. PILLAI, K. J. DOUGHERTY;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: The spinal cord contains the neuronal network that generates the rhythmic and patterned basis of locomotion. This includes putative rhythm generating interneurons (INs) that express transcription factor Shox2. Locomotor rhythm generation likely arises from a combination of intrinsic cellular properties and network interactions. Approximately ¼ of Shox2 INs in the adult spinal slice demonstrate voltage-dependent spontaneous oscillations in the absence of any pharmacologic manipulation, indicating conditional bursting properties. Various currents implicated in neural rhythmogenesis are present in adult Shox2 INs, suggesting potential contributions of ionic mechanisms in shaping adult Shox2 IN rhythmogenesis. In the present study, we tested the hypothesis that ionic currents and other intrinsic properties could be used to differentiate between spontaneously rhythmic and non-rhythmic adult Shox2 INs. Using whole-cell patch clamp recordings from adult Shox2 INs in lumbar spinal slices from Shox2cre; R26-IsI-tdTomato mice, we found that ~23% of Shox2 INs displayed spontaneous oscillations, most prominent when held between -40 to -60mV with bias current. Voltage and current clamp protocols were used to measure intrinsic properties and parameters of various ionic currents in both rhythmic and non-rhythmic Shox2 INs. This data was entered into a principal component analysis (PCA). Rhythmic and non-rhythmic Shox2 INs were labeled on the PCA post-hoc, and were visually distinguishable on a 2D plot, primarily separated on PC1. The strongest contributors to PC1 included sustained depolarization duration, and persistent inward current (PIC) amplitude and voltage onset, which were found to be longer, larger, and more hyperpolarized in rhythmic Shox2 INs, respectively. Additionally, action potentials of rhythmic Shox2 INs were more likely to have a slow afterhyperpolarization (sAHP) mediated by calcium-dependent potassium currents (I_{KCa}), but the sAHP was larger in non-rhythmic Shox2 INs that displayed it. Because sustained depolarizations were exclusive to rhythmic Shox2 INs and the calcium-activated nonspecific cation current (I_{CAN}) underlies similar plateau potentials in other rhythmic neurons, we investigated the contributions of I_{CAN} to Shox2 IN rhythmicity. We found that pharmacological blockade of I_{CAN} during spontaneous oscillations ceased and/or disrupted bursting in all neurons tested, indicating involvement of I_{CAN} in the generation of rhythmic oscillations in adult Shox2 INs. Thus, our data implicate PIC, I_{KCa}, and I_{CAN} in Shox2 IN rhythmogenesis.

Disclosures: D. Pillai: None. **K.J. Dougherty:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.16/EE29

Topic: F.07. Rhythmic Pattern Generation

Title: Connectivity of molecularly-defined inhibitory microcircuits in Bötzinger Complex

Authors: *J. J. SKACH;
Rosalind Franklin Univ. Interdepartmental Neurosci. Phd Program, North Chicago, IL

Abstract: The Bötzinger Complex (BötC) has been described as a density of highly interconnected glycinergic and GABAergic cells with expiratory modulated activity located ventral to the nucleus ambiguous (NA), caudal to the facial nucleus (VII), and rostral to the preBötzinger Complex. However, a rigorous description of these populations and their distribution remain lacking. The functional significance of the BötC also remains unresolved as proposed roles span inspiratory gating, respiratory phase switching, and coordinating breathing with orofacial motor behaviors. One factor that may explain these disparate interpretations is that anatomical and functional investigations often rely on site-wide interventions that otherwise obscure specific connectivity and contributions of unresolved BötC microcircuits. To provide a thorough description of this region while maintaining cellular resolution, we used double reporter transgenic mice to characterize the pairwise spatial distribution and level of co-expression of BötC neurons expressing either tdTomato or EGFP in glycinergic ($GlyT2^+$), GABAergic ($GAD1^+$ or $GAD2^+$), or Dbx1-derived ($Dbx1^+$) neurons, a subpopulation critical for breathing. We found most neurons within the BötC region are $GlyT2^+$ and are ventromedial relative to NA. $GAD2^+$ neurons seem to have no spatial bias and are evenly distributed ventral to NA. $GAD1^+$ neurons are comparatively spatially restricted, confined to the region directly ventral to NA and caudal to VII. The majority of $GAD1^+$ neurons also expressed GlyT2 and GAD2. To determine if molecularly-defined BötC subpopulations could be distinguished based on efferent connectivity, we injected the retrograde tracer fast blue into the phrenic motor nucleus, a known spinal target of BötC. We found that most phrenic-projecting neurons within the BötC were $GlyT2^+/GAD1^-$, and located ventromedial to NA. To assess the afferent connectivity to these $GlyT2^+$ bulbospinal neurons, we injected a helper virus into the BötC and a G-deleted rabies virus into the phrenic nucleus of GlyT2-Cre mice which yielded a robust signal in the lateral nucleus of the solitary tract (NTS). We therefore suggest that BötC may be divided into a rostral $GAD1^+/GlyT2^+/GAD2^+$ subpopulation, a ventromedial $GlyT2^+/GAD2^+$ subpopulation, and a ventrolateral $GAD2^+$ subpopulation. The ventromedial $GlyT2^+/GAD2^+$ subpopulation contains a subset of neurons that receive monosynaptic inputs from the NTS and project to the phrenic nucleus. In conclusion, our observations point to anatomically and molecularly separable BötC microcircuits that make distinct contributions to the breathing motor program.

Disclosures: J.J. Skach: None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

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Topic: F.07. Rhythmic Pattern Generation

Support: NSFC Grant 32471187
NSFC Grant 32171129

Title: Chronic Exercise-Induced Neuronal Plasticity in the Mouse Midbrain and Spinal Cord

Authors: *L. YANG[1,2], Y. CHENG[3], Y. DAI[4];
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Abstract: Limb movements in mammals are coordinately controlled by the midbrain locomotor center and the spinal cord neural network. Although studies have shown that chronic exercise improves motor performance in mice, the mechanisms by which exercise regulates neuronal plasticity in the midbrain and spinal cord remain unknown. In this study, using whole-cell patch-clamp recording combined with neuronal imaging techniques, we systematically evaluated the effects of three-week treadmill training on the excitability and morphological plasticity of neurons in the mesencephalic locomotor region (MLR) and the lumbar spinal cord (SC) of day-21 mice with acute brain slice and spinal cord slice preparations. Our results showed that exercise training significantly enhanced the excitability of MLR and spinal neurons, as reflected by a reduced rheobase and hyperpolarization of the action potential threshold. Meanwhile, persistent inward currents (PICs) were markedly potentiated, with a lower activation voltage and increased amplitude. Pharmacological analysis further revealed that sodium-mediated and calcium-mediated components of PICs differentially regulated neuronal firing properties. In addition, exercise training promoted dendritic remodeling, characterized by significant increases in total dendritic length, branch number, and terminal number. Comparative analysis demonstrated that both functional and structural plasticity were significantly greater in spinal neurons than in MLR neurons. Within the spinal cord, ventral horn neurons exhibited more pronounced adaptations than dorsal horn neurons. Correlation analysis further revealed significant associations between dendritic remodeling, PIC enhancement, and increased neuronal excitability. Collectively, these findings indicate that chronic exercise training induces neural plasticity at multiple levels of the motor system, with the spinal cord network displaying greater adaptive capacity than the brainstem locomotor center. This study highlights the spinal motor system as a potential key target for exercise-induced neural remodeling and provides new evidence for understanding the multi-level adaptive mechanisms of the motor system.
Keywords: Exercise Training; Neural Plasticity; Mesencephalic Locomotor Region; Spinal Cord; Persistent Inward Currents

Disclosures: L. Yang: None. **Y. Cheng:** None. **Y. Dai:** None.

Poster

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Program #/Poster #: PSTR366.18/EE31

Topic: F.07. Rhythmic Pattern Generation

Support: NSFC Grant 32471187
NSFC Grant 32171129

Title: Ion Channel Mechanisms Regulating Frequency-Current Relationship and Exercise Endurance in Rat Spinal Motoneurons

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Abstract: The firing frequency of spinal motoneurons (MNs) exhibit acute and chronic exercise dependence, yet the underlying ion channel mechanisms remain incompletely understood. This study investigated the modulatory roles of voltage-gated potassium, calcium, and sodium channels on MN firing frequency, fictive locomotor rhythm, and exercise endurance. Whole-cell patch-clamp recordings were performed on spinal cord slices from postnatal day 1-10 Wistar rats to assess MN frequency-current (F-I) relationships. Isolated spinal cord ventral root recordings were used to evaluate step frequency and electroneurogram (ENG) amplitude during fictive locomotion. Swim-to-exhaustion tests examined the effects of calcium channel drugs on exercise endurance. Patch-clamp data showed that TEA (5 mM) decreased F-I slope, left-shifted the x-intercept, and enhanced excitability. Nimodipine (25 μM) increased slope and right-shifted the intercept. Bay K8644 (5 μM) left-shifted the intercept. Riluzole (2 μM) reduced slope. Veratridine (1 μM) reduced slope and left-shifted the intercept. Ventral root recordings revealed that TEA (5 mM) increased fictive step frequency. Riluzole (2 μM) decreased step frequency and ENG amplitude. Veratridine (1 μM) increased step frequency. Nimodipine (25 μM) decreased both step frequency and ENG amplitude. Bay K8644 (5 μM) increased ENG amplitude but decreased step frequency. Swim tests demonstrated that intraperitoneal nimodipine (5 mg/kg) significantly reduced time to exhaustion, whereas Bay K8644 (2 mg/kg) prolonged it. Collectively, MN firing frequency is differentially modulated by potassium, sodium, and calcium channels, with calcium channels playing a dominant role in regulating exercise endurance, highlighting them as key targets for motor function modulation.

Disclosures: Y. Cheng: None. **Y. Dai:** None.

Poster

PSTR366: Rhythmic Pattern Generation: Cellular Properties and Connectivity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.19/EE32

Topic: F.07. Rhythmic Pattern Generation

Support: NSFC Grant 32471187
NSFC Grant 32171129

Title: A Study on Spinal Motor Control and Skeletal Muscle Force Computation Based on Ion Channel Mechanisms

Authors: *Y. DAI[1], Y. CHENG[2];
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Abstract: Spinal motoneuron excitability undergoes profound changes during acute and chronic exercise. The ion channel-driven alterations in neuronal excitability improve the efficiency, accuracy and strength of motor control executed by the spinal neural network known as central pattern generator (CPG). Still, the underlying neural mechanisms remain elusive, and the core questions are as follows: (1) How does ion channel modulation of neuronal excitability regulate motoneuron pool recruitment? Do different types of motoneuron pools differ in recruitment intensity and locomotor rhythm? (2) How are different types of motoneuron pool outputs converted into skeletal muscle force production, and how do these outputs shape the timing, phase, intensity and rhythm of locomotion? To address these issues, we constructed a spinal motor system model using experimental data, which integrated three functional modules: the CPG module, the spinal ventral root electroneurogram (ENG) module, and skeletal muscle force computation module. Specifically, models of spinal interneurons (excitatory and inhibitory neurons) and motoneurons (S- and FR-type) were constructed using the compartment model and cable theory, while six types of ion channels (NaT, NaP, L-type Ca, K(Ca), K(DR) and K(leak)) were developed based on the Hodgkin-Huxley (H-H) model. This system model faithfully reproduced the characteristics of the mammalian (feline) spinal neural networks and the alternating activation of flexor and extensor half-centers. Key simulation results are summarized: (1) Increasing conductance of NaP, NaT and L-type Ca, or decreasing K(Ca) conductance, markedly speeded up locomotor rhythm and boosted muscle force output, with divergent regulatory effects across ion channel subtypes. (2) NaP and K(Ca) primarily governed stepping frequency; NaT and L-type Ca controlled the instantaneous firing rate of rhythmic discharges, ENG amplitude and muscle force. K(Ca) and L-type Ca were the major determinants of stable gait alternation. (3) Ion channels exerted similar modulatory effects on S-type and FR-type motoneuron pool recruitment and muscle force. Under the same ionic modulation, however, FR pools produced higher ENG amplitude and greater muscle force than S-type pools. This study provided experimental evidence and design principles for constructing ion channel-enabled brain-like intelligent motor control systems.

Disclosures: Y. Dai: None. **Y. Cheng:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.01/FF1

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Grants-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Science (JSPS) 23K14439
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LEGEND Research Grant Program 2024 from Bio Legend Japan

Title: Comparative analysis of human and mouse sexually dimorphic nuclei supports the mouse SDN-POA as a model for fetal testosterone-linked behavioral variation

Authors: *M. MORISHITA, I. AIBA, K. SEKIYA, H. ISHII;
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Abstract: Sexually dimorphic nuclei (SDNs) in the human preoptic/anterior hypothalamic region and bed nucleus of the stria terminalis (BNST) have been discussed in relation to sexual orientation and gender identity, respectively, but their correspondence to mouse SDNs remains unclear, limiting mechanistic studies. All procedures involving human tissue and animals were approved by the relevant institutional ethics committees. We performed comparative immunohistochemical analysis of human and mouse brain sections. The human uncinate nucleus (Unc; INAH3/4) and mouse SDN of the preoptic area (SDN-POA) both contained calbindin-D28K (Calb)-positive and GABAergic neurons and showed male-biased volume and neuron number, whereas the human intermediate nucleus (INAH1/2) had a distinct marker profile and no detectable sex difference. These features identified the Unc as the human nucleus most closely resembling the mouse SDN-POA. In the BNST, the human central subdivision (BNSTc) contained Calb-positive neurons and VIP/CRF-positive fibers, with male-biased volume. Because Calb marks the mouse BNST principal nucleus and VIP/CRF mark the oval nucleus, the human BNSTc appears to integrate features of multiple mouse subnuclei rather than matching a single structure. We next asked whether these mouse SDNs relate to partner preference. In adult male mice, female-directed preference in a three-chamber test correlated with SDN-POA volume, Calb-positive neuron number, and c-Fos expression, whereas the BNST subnuclei analyzed showed no comparable relations. Given prior reports linking the human Unc to sexual orientation, we focused on the SDN-POA and examined how individual differences in this nucleus arise during development. Amniotic testosterone was measured in male fetuses at embryonic day 18.5, and the preoptic area of males with high or low fetal testosterone was analyzed by RNA-seq, quantitative PCR, and *in situ* hybridization. High-testosterone males showed higher expression of genes involved in GABAergic neuron development and greater accumulation of *Arx*-expressing neurons within the SDN-POA than low-testosterone males. Selected males were then raised to adulthood for partner preference and SDN-POA analyses. Males with higher fetal testosterone later showed stronger female-directed partner preference and larger SDN-POA structures. By integrating human-mouse comparative anatomy with longitudinal mouse analyses, these findings support the mouse SDN-POA as a tractable model for studying developmental variation in a brain nucleus relevant to partner preference.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.02/FF2

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: JSPS KAKENHI 20K06467
JSPS KAKENHI 23K05612
Sanford Research (to I.M.)
Intramural Research Grants for Neurological and Psychiatric Disorders of NCNP (3-9, 6-9)

Title: Genome editing-based refinement of GPCR visualization in mice using the oxytocin receptor as a model

Authors: *Y. U. INOUE[1], E. KURUMIYA[2], R. TANY[2], E. KOIKE[1], J. ASAMI[1], I. MASUHO[2,3], T. INOUE[1];
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Abstract: Oxytocin is a key neuromodulator that regulates a wide range of social, sexual, and parental behaviors. Although the neural actions of oxytocin critically depend on the spatial distribution of the oxytocin receptor (Oxtr), direct visualization of endogenous Oxtr protein in the brain remains challenging because this G protein-coupled receptor (GPCR) exhibits poor antigenicity and is often expressed at low levels. We previously generated epitope-tagged Oxtr knock-in mice and demonstrated their utility for receptor visualization (Inoue YU et al., eNeuro 0423-21, 2022). However, their sensitivity was insufficient for comprehensive detection of Oxtr across brain regions, developmental stages, and subcellular compartments. Here, we systematically refine genome editing-based tagging strategies to develop an improved Oxtr reporter mouse. We compared the conventional triple-HA tag with two recently developed high-sensitivity tags, Spaghetti Monster fluorescent protein (smFP) and the ALFA tag, each fused to the Oxtr C-terminus. *In vitro* G protein activation assays showed that all variants retained ~70% of wild-type activity, consistent with AlphaFold 3 structural predictions. We then generated knock-in mouse lines carrying each tagged receptor at the endogenous Oxtr locus and evaluated *in vivo* performance. Among the tested designs, smFP markedly improved detection sensitivity and signal-to-noise ratio while preserving receptor localization, whereas ALFA impaired receptor trafficking without enhancing detectability. The Oxtr-smFP line enabled robust detection of endogenous Oxtr expression in the adult brain, which was difficult to visualize in our previous reporter model. Additionally, primary cultured neurons derived from this line showed Oxtr distribution along dendrites, down to their terminals, at subcellular resolution. These findings establish the Oxtr-smFP mouse as a valuable resource for studying oxytocin signaling in neural circuits underlying social interaction, parental care, and other neuroendocrine

behaviors, while providing a general framework for improved *in vivo* visualization of endogenous GPCRs. For further details, see Inoue YU et al., Scientific Reports (2026).

Disclosures: Y.U. Inoue: None. **E. Kurumiya:** None. **R. Tany:** None. **E. Koike:** None. **J. Asami:** None. **I. Masuho:** None. **T. Inoue:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.03/FF3

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: AOA Postgraduate Fellowship Award
NIH grant K99 DA056573
Stanford Wu Tsai Neurosciences Institute
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Title: Serotonin Exerts Opposing Effects on Social Behavior Through Distinct Striatal Circuits

Authors: *M. X. LI[1], A. P. F. CHEN[1], M. B. POMRENZE[1], M. Y. GUO[2], S. RAO[1], J. BAEK[1], L. LUO[1], R. C. MALENKA[1];
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Abstract: Serotonin (5-HT) is a critical modulator of social behavior, yet the circuit and molecular mechanisms through which it exerts its many effects remain poorly understood. The paradoxical observation that serotonergic agents can both promote prosocial outcomes and induce social anxiety suggests that 5-HT may act through functionally distinct pathways. Here we show that dorsal raphe nucleus (DRN) serotonergic projections to the nucleus accumbens (NAc) and tail of the striatum (TS) exert bidirectional and opposing control over social behavior. Anterograde and retrograde tracing revealed that the DRN densely innervates both regions through largely non-overlapping projection neurons. Optogenetic activation of 5-HT terminals in the NAc increased social preference, while activation in the TS decreased social preference. Retrograde Cre-mediated Tph2 knockout of serotonin signaling confirmed opposing roles: disrupting NAc serotonergic input reduced sociability, while disrupting TS input enhanced it. Spatial transcriptomic analysis revealed TS enrichment of Htr2a expression in striatal medium spiny neurons, particularly in D1R-expressing cells, whereas Htr1b expression was broadly distributed. Consistent with these receptor expression patterns, infusion of a 5-HT2A agonist into the TS of serotonin-deficient mice rescued their antisocial phenotype, while a 5-HT1B agonist infused into the NAc restored prosocial behavior. Fiber photometry recordings from D1R-expressing MSNs demonstrated that 5-HT1B agonism suppresses NAc D1-MSN activity during social encounters, while 5-HT2A agonism increases TS D1-MSN activity. Together, these findings reveal a circuit architecture in which a single neuromodulatory system exerts opposing

behavioral effects through anatomically and molecularly distinct striatal targets, with direct implications for understanding the pleiotropic behavioral effects of serotonergic drugs.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.04/FF4

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: JSPS Grant 21H04981
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Sponsored Research Grant from Kao-Corporation
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Title: Music-mediated interaction enhances behavioral predictability and frontal theta inter-brain synchrony linked to infant cardiac recovery

Authors: *Y. TANAKA[1], T. DAIKOKU[2], K. HONDA[3], S. MATSUMURA[3], M. KASHINO[3], M. MYOWA[1];
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Abstract: In everyday caregiving, musical interaction temporally organizes multimodal cues (singing, movement, touch, gaze) through beat, phrasing, and repetition (Malloch & Trevarthen, 2009; Trehub, 2003; Lense et al., 2022). Such temporal regularity may increase cue predictability and promote parent-infant neurophysiological synchrony, but this link remains under-tested. Furthermore, since the infant central nervous system is still developing, autonomous recovery from physiological deviations after unpredictable events is limited, requiring behavioral and neurophysiological co-regulation with caregivers (Atzil et al., 2018; Abney et al., 2021). Given that co-regulation varies across dyads and is shaped by shared interactional experience (Diaz-Rojas et al., 2025), dyads with greater music-related increases in inter-brain synchrony may show enhanced infant recovery from prediction errors. Yet how music-mediated interaction links behavioral predictability, inter-brain synchrony, and infant autonomic recovery remains unclear. We examined whether a one-week home-based music interaction experience altered these processes. Participants were 48 Japanese mother-infant

dyads (infants: 24 boys; age: M = 236.58 days, SD = 19.67). In the Interaction (INT) condition, dyads engaged in face-to-face play with two unfamiliar songs for 7 days; in the Background (BG) condition, they listened to two other songs for equal duration without social interaction. The following day, dyads played with songs from both conditions in the laboratory, while simultaneous EEG, ECG, and video were recorded. Mother/infant behaviors were coded every 1 s. A Hidden Markov Model (C = 2, K = 14) was fitted to the 8-channel behavioral stream; Surprise indexed behavioral unpredictability. Inter-brain synchrony was quantified using weighted phase-lag index (wPLI; theta: 3-6 Hz; alpha: 6-9 Hz) in 2-s epochs locked to Surprise peaks. Infant RR-interval (RRI) epochs spanned −4 to +4 s around each peak. We found that INT showed lower mean Surprise than BG ($t(47) = 2.267$, $p = .028$, $dz = 0.327$). Before peaks, frontal theta inter-brain synchrony was higher in INT than BG ($\Delta \approx 0.045$, $dz \approx 0.74$), with a similar alpha effect ($\Delta \approx 0.028$, $dz \approx 0.63$). Infant RRI showed a V-shaped mobilization-recovery pattern around Surprise peaks in both conditions. Critically, the INT-BG difference in pre-peak frontal theta wPLI predicted the INT-BG difference in subsequent infant RRI recovery ($\beta = 3.46$, $p = .043$). These findings suggest that music-mediated interaction enhances behavioral predictability and frontal theta inter-brain synchrony, supporting infant autonomic recovery after unpredictable events.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.05/FF5

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Voluntary Wheel Running in Mice Reduces Competition-Based Agonistic Behaviors

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Abstract: Social interaction is a conserved, core feature of mammalian behavior required for survival. In natural contexts, social interaction often occurs in the presence of high levels of exercise. However, scant work has been conducted to understand how exercise affects social relationships. To explore how exercise impacts social behavior and its neural underpinnings, we chose to study voluntary wheel running (VWR) in pairs of mice, a species that naturally forms social groups and exercises voluntarily. First, we housed male and female 8-week-old C57Bl/6J mice in same sex pairs (n=30-32 pairs/condition/sex) with either locked running wheels or unlocked running wheels for six weeks before beginning social behavioral testing using a food pellet competition test (FCT). In the FCT, an appetitive food pellet was placed into the homecage of a pair of mice and attempted food stealing behavior as quantified as a measure of agonism during competition. Pairs of mice housed with unlocked wheels displayed a 1.905-fold reduction

across sexes in agonistic stealing attempt time compared to pairs housed with locked wheels. We next expanded on these findings by asking whether exercise could have similar benefits if available for a more restricted time period. We again same-sex pair housed mice (n = 10/sex/condition), but restricted their running wheel exposure (locked or unlocked wheel pairs) to 6 hours/day for 5 days/week in a novel cage. After 6 weeks, we conducted the FCT as well as an additional competition task: the warm spot competition task (WST). In the WST, cagemate pairs were placed in an empty cage with a cold floor except for a small heated warm spot, large enough for only 1 mouse. Attempted displacement of cagemate by pushing to gain possession of the warm spot was quantified as a measure of agonism during competition. Pairs that visited unlocked wheels displayed a 2.33-fold reduction in time attempting to steal the food pellet in the FCT and a 2.89-fold reduction in time attempting to displace their cagemate in the WST in males than those that visited locked wheels. Combined, our results suggest that exercise drives a reduction in agonistic behaviors during competition in both sexes, even when wheels are only available for time-limited, weekday sessions. Ongoing work is focused on assessing neuronal activity of brain regions associated with social behavior using c-Fos expression in brains from mice perfused after 4h of wheel exposure in both sexes. Loneliness and poor social relationships are pervasive issues in humans that contribute to declines in mental and physical health. Our work demonstrates that social exercise may be a novel treatment avenue for enhancing social relationships.

Disclosures: W.C. Butke: None. **B. Smith:** None. **E.D. Kirby:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.06/FF6

Topic: G.02. Neuroendrocrine Processes and Behavior

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Title: Synaptic plasticity-related genes mediate the relationship between social networks and neuroanatomy in the superior temporal sulcus

Authors: *S. D. FINGER[1], Y. YE[2], M. J. MONTAGUE[3], T. CAYO BIOBANK RESEARCH UNIT[5], A. D. MELIN[6], J. HIGHAM[7], L. BRENT[8], M. L. PLATT[4], C. TESTARD[9], J. SALLET[10], A. DECASIEN[11], N. SNYDER-MACKLER[12], K. CHIOU[1];
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Abstract: Social connections influence health and longevity in primates and are thought to have played a role in primate brain evolution. However, the molecular drivers of variation in brain anatomy, particularly in regard to the influence of the social environment, remain largely unknown. Here, we use data from free-ranging, behaviorally phenotyped rhesus macaques to test the effects of social hierarchy and connectedness on molecular and structural neuroanatomical phenotypes. We paired transcriptomic and MRI data collected across 15 brain regions from 36 macaques (20F, 16M) spanning adulthood. In one socially relevant brain region, the superior temporal sulcus (STS), social connectedness was strongly associated with gene expression (n=2,450 DEGs, LFSR < 0.05)-enriched for genes involved in learning, memory, and stress processing ($P < 0.01$). Focusing on the STS, we then conducted mediation analyses to probe how gene expression is linked to the association between social connection and brain structure; identifying 27 genes that significantly mediate the link between social variation and STS volume ($P < 0.05$). These mediating genes were enriched for pathways related to synaptic plasticity, anatomy and development ($P < 0.05$). Our study offers powerful potential for illuminating precisely how social connections ‘get under the skin’ to shape brain structure and function in primates.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.07/FF7

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: KAKEN 23K10598

Title: Environmental Modulation of Daily Physical Activity Patterns and Monoaminergic Adaptation in Rats

Authors: *S. YANAGITA[1], N. KUBOTA[2];
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Abstract: Enriched environments (EE) provide an experimental framework for examining how daily physical activity patterns shape behavioral and neurobiological adaptation; however, the contribution of environmental spatial structure to health-related activity remains insufficiently understood. This study investigated how vertical versus horizontal space expansion within EE influences spontaneous daily movement, functional activity patterns, and monoamine regulation in rats. Male Wistar rats (4 weeks old, N = 24) were housed for four weeks under sedentary, standard EE, multi-story EE (Multi-EE), or wide-floor EE (Wide-EE) conditions. Locomotor, climbing, and postural activities were continuously monitored using mobile accelerometers and analyzed as indicators of habitual physical activity across light-dark cycles. Brain monoamine levels, including serotonin and dopamine, were quantified using high-performance liquid chromatography, and peripheral functional indices, including body weight, adrenal mass, and soleus muscle mass, were evaluated. Compared with Wide-EE, Multi-EE animals showed lower total locomotor distance but displayed frequent vertical movements and sustained postural adjustments, reflecting functionally relevant daily activity rather than exercise-oriented behavior. Despite reduced horizontal movement, Multi-EE rats exhibited enhanced serotonin-related indices in multiple brain regions and maintained stable peripheral function. Importantly, qualitative aspects of daily movement, such as posture changes and vertical transitions, were closely associated with monoaminergic modulation alongside overall activity volume, suggesting that both the quantity and quality of daily movement contribute to neurochemical adaptation. These findings indicate that environmentally induced daily physical activity patterns support brain monoamine regulation and functional resilience. Vertical environmental complexity may promote health-related movement behaviors relevant to rehabilitation, aging, and chronic disease management, emphasizing the importance of designing environments that encourage sustainable everyday activity for long-term mental and physical well-being and offering insights into strategies to counteract sedentary lifestyles in modern societies.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR367.08/FF8

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NSF Grant IOS-2421958

Title: Characterizing Androgen and Social Behavior Relationships in Spiny Mice Groups

Authors: *C. LEE[1], C. ESQUILIN-RODRIGUEZ[1], N. GOSE[1], J. P. CURLEY[2], A. KELLY[1]; [1]Emory Univ., Atlanta, GA; [2]Psychology, Univ. of Texas At Austin, Austin, TX

Abstract: Steroid hormones are long established modulators of social behaviors ranging from social learning and recognition to aggression. Although well-described for estrogens, fewer studies have described the function of androgens like testosterone (T) or androgen receptors (AR) for social behaviors, and even fewer have investigated their role in female organisms. Thus, we aimed to investigate androgen and social behavior relationships in both male and female organisms in the non-territorial spiny mouse (Acomys dimidiatus). We established 5 mixed-sex groups of 7 spiny mice each (n = 35) that were introduced to a novel, enriched environment and recorded for 5 hours over the course of 4 days. Blood and brain samples were collected after the final day of behavioral observations to observe plasma T levels and AR cell densities in the ventromedial hypothalamus (VMH). Behavior was scored every 5 minutes of behavioral recordings for a total of 240 timepoints per animal. T-tests revealed that male spiny mice have significantly higher plasma T levels and VMH AR cell densities than female spiny mice ($p < 0.05$). Pearson's correlations revealed that there was no significant correlation between plasma T levels or VMH AR cell densities and observed social behaviors or David's score ($p > 0.05$). Assortativity analyses indicate that individuals with a higher David's score, and thus are more dominant, show more dominance behaviors towards subordinates ($p = 0.04$), but David's score does not influence affiliative or investigative behaviors. In addition, no other attributes (kin, sex, AR cell densities, plasma T levels) influence who an individual mouse interacts with. These findings suggest that dominance behaviors and status in spiny mice do not influence or are not influenced by androgens, which is not a common finding in the literature on androgens and dominance. However, it is important to consider methodological differences in the literature, the potential role of other steroid hormones in dominance, and the low overall occurrence of dominance in our current dataset. Despite this, we are contributing to a growing body of literature examining androgen-social behavior relationships in both male and female organisms.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR367.09/FF9

Topic: G.02. Neuroendrocrine Processes and Behavior

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NINDS 5T32NS 86750

Title: A parvocellular oxytocin subpopulation gates caregiving toward sick individuals

Authors: *A. CASLIN[1], K. QUIÑONES-LARACUENTE[3], G. KAUR[4], K. M. O'NEIL[5], J. BASU[2], R. C. FROEMKE[6];
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Abstract: Maternal care is critical for offspring well-being and must be directed and flexible depending on the perceived needs of young. It remains unclear which neural mechanisms are necessary for mothers to sense and respond to those needs. Sickness behaviors may serve as socially useful signals that solicit comfort or caregiving, and the context of maternal care may reinforce those responses. Here, we use spontaneous and trial-based behavioral tests, optically-tagged *in vivo* electrophysiology, and intersectional chemogenetics to determine how the mouse oxytocin system contributes to approach toward sick pups. We characterized maternal behavior of a mouse dam toward P14 pups injected with lipopolysaccharides (LPS, 1 mg/kg) or saline over the course of four hours using a multi-camera longitudinal behavioral monitoring system developed in the lab. Dams exhibited increased huddling toward LPS-injected pups within the first two hours after sickness induction (N=6-7 per group, p=0.041). Dam presence also rescued sickness-induced locomotor deficits (N=2-4 per group, p=0.0385). To determine whether this approach was dam-initiated, we tested dams in a three-chamber social preference assay. Dams spent more time in the chamber containing a familiar LPS-injected pup than in the chamber with the saline-injected pup (N=8, p=0.013). Individual sensory cue testing revealed that approach requires multiple sensory modalities to overcome the aversive signal carried by sickness cues. Using silicon probe recordings coupled with a fiber for blue light delivery in the paraventricular nucleus of the hypothalamus (PVN) of Oxt-Flp female mice expressing Flp-dependent ChR2, we examined how oxytocin neuron activity changes in response to sick versus healthy pups. Oxytocin neurons exhibited a selective increase in firing that preceded approach toward sick pups (n=78 oxytocin units, n=80 unIDd units for 6 sessions, N=4 mice, p=0.01) which could predict dam choice on individual trials (oxytocin units: $p<0.0001$; all units: p=0.002; unIDd units: p=0.112) and scaled with degree of preference (Spearman r=0.9, p=0.037; bootstrap p=0.008). Given response heterogeneity across the population, we generated intersectional transgenic lines to target the two major oxytocin neuron subtypes, magnocellular and parvocellular. Inhibition of parvocellular, not magnocellular, neurons prevented sick pup approach (Parvo CNO vs. Parvo Veh: p=0.01, N=5, Magno CNO vs. Magno Veh: p=0.34, N=6). Together, these data suggest that parvocellular oxytocin neurons gate familiarity-dependent approach toward sick pups with anticipatory recruitment enabling approach over avoidance.

Disclosures: A. Caslin: None. **K. Quiñones-Laracuente:** None. **G. Kaur:** None. **K.M. O'Neil:** None. **J. Basu:** None. **R.C. Froemke:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.10/FF10

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Midwestern University Intramural Grant

Title: Visual exposure to seizure-like behavior induces social disengagement without stress contagion in zebrafish

Authors: A. HALKOR, C. A. HOWELL, B. VERA COVARRUBIAS, ***J. A. KAUFMAN**; Midwestern Univ., Glendale, AZ

Abstract: Emotional contagion, the social transmission of affective states between individuals, has been demonstrated in zebrafish exposed to conspecifics exhibiting antipredator responses. However, it remains unclear whether contagion reflects a generalized sensitivity to conspecific distress or depends upon the perception of ethologically meaningful social cues. To address this question, adult zebrafish were tested in a demonstrator-observer paradigm. Demonstrators received either reverse-osmosis water or pentylenetetrazole (PTZ), a convulsant that induces seizure-like behavior, while both demonstrator and observer behavior were simultaneously quantified. Control demonstrators/observers (n = 14 each) and PTZ demonstrators/observers (n = 16 each) were housed in adjacent tanks that permitted visual communication but prevented water exchange, restricting social information transfer to visual cues. Whole-body cortisol concentrations were measured in demonstrators and observers (n = 6 pooled samples/group). PTZ-treated demonstrators exhibited robust increases in freezing, bottom-dwelling, darting, and whole-body cortisol relative to controls. In contrast, observers exposed to PTZ-treated demonstrators did not exhibit increased freezing, bottom-dwelling, darting, or cortisol compared with control observers. However, PTZ observers spent less time in close proximity to demonstrators, suggesting social disengagement despite the absence of behavioral or endocrine stress transfer. Group differences were evaluated using Kruskal-Wallis tests followed by Dunn's multiple comparisons. These findings indicate that pathological motor disturbance is insufficient to induce behavioral or endocrine stress contagion in zebrafish despite producing a robust demonstrator phenotype, contrasting with previous studies using ethologically relevant antipredator cues. The results support a cue-dependent model of affective state transmission in which emotional contagion depends on the interpretation of biologically relevant social signals rather than generalized sensitivity to abnormal conspecific behavior.

Disclosures: A. Halkor: None. **C.A. Howell:** None. **B. Vera Covarrubias:** None. **J.A. Kaufman:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.11/FF11

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Effect of single or repeated prior stressful stimuli on psicoemotional responses in the Open Field Test and Elevated Plus Maze in rats

Authors: E. QUINTO MORALES[1], M. MARTINEZ ROMERO[2], E. PÉREZ SEPÚLVEDA[3], R. RODRÍGUEZ ARELLANES[3], *A. SALDIVAR-GONZALEZ[4];
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Abstract: Anxiety disorders affect approximately 359 million people worldwide and represent a major public health concern. However, the mechanisms underlying anxiety-related behaviors remain incompletely understood. To investigate the effects of single and repeated stressful events on anxiety-like responses, male Wistar rats (250-300 g) were used. Animals were housed under a reversed 12 h light-dark cycle (lights off: 08:00-20:00) with *ad libitum* access to food and water. Behavioral testing was conducted two hours after the onset of the dark phase in a dimly lit red room by a trained observer blinded to treatment conditions. All procedures were approved by the local ethics committee and complied with federal guidelines for the care and use of laboratory animals. Before behavioral testing, rats received either a single or repeated mild electric paw shock and were evaluated after short or long post-stimulus intervals. Anxiety-like behavior was assessed using two well-established paradigms: the Open Field Test (OFT), in which locomotor activity and exploratory behavior (crossings and rearings) were recorded, and the Elevated Plus Maze (EPM), in which the number of transitions between sections and the time spent in the open arms were measured. Repeated exposure to brief electric paw shocks followed by behavioral assessment produced no significant changes in locomotor activity. Similarly, a single acute shock administered 30 min before testing did not affect locomotion in either the OFT or the EPM. In contrast, stressed animals exhibited enhanced exploratory behavior, as evidenced by increased rearing in the OFT and increased time spent in the open arms of the EPM. These findings indicate that acute stress does not impair general locomotor function but induces behavioral changes consistent with heightened exploratory activity and altered emotional reactivity. Altogether, the results suggest that prior exposure to mild stressful stimuli increases arousal and may promote adaptive behavioral responses to biologically relevant environmental cues, such as food availability, predator detection, or reproductive opportunities.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

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Title: Neurobiological Mechanisms Underlying Experience-Dependent Social Preferences During Early Postnatal Life

Authors: *I. NWABUDIKE[1,2], A. CHE[2];
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Abstract: During early postnatal development, animals form social affiliations that are shaped by their immediate environment and, in turn, regulate long-term social engagement with other individuals. These social bonding processes may be disrupted in various neurodevelopmental and neuropsychiatric disorders such as Autism Spectrum Disorder and schizophrenia. However, there is limited understanding of the mechanisms through which experience-dependent developmental social affiliations are represented in higher-order circuits relevant to emotional and cognitive function during infancy and early adolescence. In this study, we tested the hypothesis that medial nucleus of the amygdala (MeA), which integrates sensory inputs and motivational state signals in adult animals, dynamically alters the social preferences of developing mice in an experience-dependent manner. Using an odor preference task for young mice across developmental stages, we found that while pups reared by female mice only show avoidance of stranger male odor when tested at postnatal day (P)21, early exposure to male social stimulus (co-reared) primes a shift from aversion to generalized attraction to stranger male odor. In addition to rearing conditions, weaning, acute isolation, and chronic intermittent developmental isolation also alter relative social odor preferences. We show that activation of MeA neurons is negatively correlated with the behavioral preference for a given social odor, and can be altered by early life experiences (prior exposure, weaning, and acute social isolation). Dual-color fiber photometry recordings of total MeA versus inhibitory neuron calcium signal during odor approach showed that MeA inhibitory neurons are preferentially activated by stranger male odors in co-reared pups with prior exposure to male social stimuli, suggesting that the suppression of MeA activation when exploring preferred odors may be controlled by local inhibition. Our results indicate that early-life experiences can dynamically alter social odor-preference through functional recruitment of MeA inhibitory neurons, exerting a lasting impact on in long-term social preference and affiliation.

Disclosures: I. Nwabudike: None. **A. Che:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.13/FF13

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: VIEP-BUAP BUAP-CA-288
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Title: Effect of Pramipexole on yawning and penile erections in High and Low Yawning rats: Exploring dopaminergic regulation

Authors: *E. LOPEZ[1], C. CORTES[2], A. UGARTE[1], J. R. EGUIBAR[3];
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Abstract: Yawning and penile erection are phylogenetically conserved behaviors that are regulated by different neurotransmitters including glutamate, oxytocin and dopamine that converge primarily in the paraventricular nucleus of the hypothalamus. It is relevant that under pharmacological or physiological stimulation, they are expressed in close association, supporting the yawning-penile erection syndrome, which is useful for preclinical investigation of the dopaminergic regulation of these behaviors. The high-yawning (HY) and low-yawning (LY) rat sublines, developed through selective inbreeding of Sprague-Dawley rats, differ in their spontaneous frequencies of both yawning and penile erections, making them an ideal genetic model to analyze differential dopaminergic effects on these behaviors. The aim of this study was to analyze the effects of the systemic administration of pramipexole, a selective dopaminergic D2 receptor agonist, on the frequency of yawning and penile erections in adult male HY and LY rats, and its correlation. Adult male rats from the HY and LY sublines received systemic administration of pramipexole (0.001, 0.01, 0.1, or 1 mg/Kg) or vehicle. Following administration, a detailed 60-minute behavioral observation in a novel environment was conducted to quantify the frequency of yawning, penile erections and related stereotypical displays such as grooming bouts. Pramipexole significantly increased yawning frequency in both sublines, with the 0.1 mg/Kg dose being the most effective, but a dose-response effect was not observed for penile erection frequency. A correlation analysis revealed a strong, positive association between yawning frequency and penile erections exclusively in the HY subline, supporting a coordinated central co-mechanism. Also, the highest dose induced a statistically significant decrease in the number of grooming bouts exclusively in the HY subline. These results substantiate the critical role of the central dopaminergic system in modulating these behaviors. Furthermore, the close correlation between yawning episodes and erectile responses highlights the validity of the yawning-penile erection syndrome in the HY rats as a sensitive tool for preclinical screening and testing novel therapeutic strategies targeting male sexual disorders, such as erectile dysfunction or premature ejaculation.

Disclosures: E. Lopez: None. **C. Cortes:** None. **A. Ugarte:** None. **J.R. Eguibar:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH R37DA031389

Title: Convergence of fast and slow inhibitorypathways onto a common target neuron orchestrates a persistent aggressive state

Authors: *Z. ZHONG[1], C. SCHRETTER[2], G. M. RUBIN[3], D. ANDERSON[1];
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Abstract: Persistent internal states must be maintained over minutes while modulating behavior on subsecond timescales, but the circuit mechanisms that enable this dual-timescale control remain poorly understood. In female Drosophila, brief activation of aIPg neurons has previously been shown to induce a minutes-long persistent aggressive state. Here, we asked how transient aIPg activation generates this persistent state and how the resulting state organizes episodic aggressive approach and attack. Using connectome-guided two-photon calcium imaging during optogenetic aIPg activation, we found that the downstream neuron TuTuA_2 exhibited the most persistent response: rapid inhibition followed by suppression that lasted for minutes after stimulation ended. Genetic and pharmacological perturbations revealed that aIPg inhibits TuTuA_2 through two convergent pathways with distinct temporal dynamics. A GABAergic pathway, relayed by the inhibitory interneuron SMP054, produced fast but transient inhibition of TuTuA_2. In parallel, aIPg-derived short neuropeptide F (sNPF) acted through Go signaling in TuTuA_2 to generate slow, persistent inhibition. Blocking either sNPF signaling or SMP054 output reduced post-stimulation aggression, indicating that both pathways are required for full expression of the persistent aggressive state. Using hidden Markov model-based behavioral analysis, we further found that these pathways regulate distinct components of the behavioral transition structure. sNPF signaling promoted transitions from approach to attack and supported reactive, target-motion-evoked approach, whereas SMP054/GABA signaling was required for proactive approach when target motion was weak or absent. Together, these results identify a dual-timescale circuit motif in which convergent slow peptidergic and fast GABAergic inhibition of a common downstream neuron, enables a persistent internal state to reshape behavioral transitions across timescales.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: National Eye Institute (NEI) 5R16EY037336-02
National Institute of General Medical Sciences (COBRE-PRCMS) 1P20GM156713-01

Title: The Impact of Darkness on the Ontogeny of Aggression in the Mexican tetra, Astyanax mexicanus

Authors: *H. A. CARDONA-SIERRA[1,2,3], A. J. RIVERA[1,2,3], A. J. MORALES[1,2,3], D. BAYRON-HO[2,3], V. DE LA ROSA-REYES[1,2], R. E. RODRIGUEZ[2,3];
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Abstract: External pressures, including temperature, light, and competition, play an essential role in the ontogeny of behaviors and are crucial for survival, adaptation, neural development, and evolution of an animal. Our lab is interested in how access to light and darkness can influence the ontogeny of aggression in fish with diverse behavioral phenotypes resulting from thousands of years of adaptation to cave habitats. To test this, we use the Mexican tetra, *Astyanax mexicanus*, a species of fish that provides a unique opportunity to study behavioral adaptation within a single species. This fish exists as two morphotypes: social, river-dwelling surface fish and blind, asocial, cave-dwelling cavefish.Our project explores whether exposure to circadian variable light cycles (14/10 light-dark cycles) and complete darkness modulates the ontogeny of aggression in *A. mexicanus*. Adapting previously published resident/intruder assays performed in adult *Astyanax*, we quantified and manually annotated emerging aggressive-like behaviors in surface fish and cavefish during juvenile development across defined developmental timepoints.Our current results in fish raised in 14/10 light-dark cycles indicate both morphotypes of *A. mexicanus* display primitive aggression through their juvenile stage. Surface fish strikes peak at 50 days post fertilization (dpf), and from 70-90 dpf strikes greatly increase. Although surface fish display double the number of strikes compared to cavefish, cavefish “aggressive-like state” lasts longer during earlier development. Under perpetual darkness, both morphotypes exhibit a decrease in striking behavior across these conditions.These findings suggest that light exposure influences the developmental trajectory of aggression within this system and provide insight into how environmental sensory experience may contribute to the developmental regulation of aggressive behavior.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

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Topic: G.02. Neuroendrocrine Processes and Behavior

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Title: The Genetics of Social Behavior: Requirement of Foxp2 in the Medial Amygdala for Male Territorial Aggression

Authors: *N. PRAKASH[1], A. SCHREIBER[1], L. HEIER[1], S. SEBAOUI[2], Y. LAHBABI[1], M. RUIZ[3], M. TEMAM[1], G. RAJU[1], T. CEPHAS[1], S. SUNDARARAJAN[3], J. CORBIN[4]; [1]Ctr. for Neurosci. Res., Children's Natl. Hosp., Washington, DC; [2]Ctr. for Neurosci. Res., Children's Natl. Hosp., District of Colombia, DC; [3]Ctr. for Neurosci. Res., Children's Natl. Hosp., Washington DC, DC; [4]Ctr. for Neurosci. Res., Childrens Natl. Hosp., Washington, DC

Abstract: Social behaviors are critical to the survival and reproductive success of animal species. Aggression, for example, is a social behavior that's key to an individual's success in competing for mates, food and defending its resources. The medial amygdala (MeA) is a key node in the social brain network regulating aggression. The MeA comprises multiple subpopulations of output neurons, one of which is marked by *Foxp2*, a transcription factor whose expression commences during embryogenesis and persists through adulthood. Prior research demonstrated that Foxp2+ neurons in the MeA in mice are necessary and sufficient for male territorial aggression. Further, whole body *Foxp2*$^{+/-}$ mice display deficits in male aggression. Based on these data, we hypothesized that *Foxp2* gene function in the MeA is essential for male territorial aggression. To test this, we assessed MeA function and male aggressive behavior in a series of *Foxp2* deletions. We found that MeA Foxp2+ cells in whole body *Foxp2*$^{+/-}$ mutants show a significant increase in soma volume but unaltered proximal dendritic arborization and neuron number and a reduction in the frequency of neuronal activity as measured by *ex vivo* calcium imaging. Analyses of viral and genetically targeted deletions of *Foxp2* reveal temporally dependent roles in male territorial aggression. Thus, *Foxp2* expression in the MeA appears to play a complex yet essential role in the programming and/or execution of male aggression.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.17/FF17

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Monmouth University Start Up Funds
NIH 1R35GM157195-01

Title: Neuronal expression of polyglutamine-expanded Ataxin-2 increases aggressive behavior in Drosophila melanogaster

Authors: V. DIAS DE OLIVEIRA[1], J. ECK[1], S. YANG[2], E. QADIRI[1], L. EYVAZZADEH[3], S. HENRY[1], O. DEMEUSE[4], B. CHOWDHURY[4], C. B. PALAVICINO-MAGGIO[5], *S. SENGUPTA[1];
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Abstract: Polyglutamine expansion in human Ataxin-2 (ATXN2) is associated with neurodegenerative diseases, including spinocerebellar ataxia type 2. Affected patients exhibit motor dysfunction as well as changes in sleep and behavioral regulation, including aggression-related behaviors. However, it remains unclear whether neuronal ATXN2-polyQ expression can directly perturb behavior-regulating neural circuits. We addressed this question in *Drosophila melanogaster* by expressing human ATXN2-polyQ in defined central brain neuronal populations using the GAL4/UAS binary expression system. Adult male flies expressing ATXN2-polyQ were tested in a food-cup based aggression assay and compared with GAL4-only and UAS-only genetic controls in age-matched male-male aggression assays. ATXN2-polyQ-expressing experimental males showed a robust increase in aggressive behavior relative to both genetic controls, with significant increases in lunge frequency and wing threat displays. In mixed-genotype assays pairing experimental males with wild-type Canton-S opponents, ATXN2-polyQ-expressing males initiated the majority of aggressive interactions and delivered most lunges, indicating the phenotype was intrinsic to the experimental animal rather than driven by reciprocal escalation. To begin mapping the relevant neurons, we combined the GAL4 driver with a UAS-mCD8::GFP reporter and observed labeled neurons in several regions of the adult central brain, including the mushroom bodies, suboesophageal ganglion, around the lateral horn. We are currently investigating courtship and sleep behavior to distinguish whether ATXN2-polyQ expression selectively increases aggression or produces broader changes in behavioral arousal. Together, these findings establish a fly model for dissecting how ATXN2-polyQ expression in defined neuronal populations alters behavior-regulating circuits, thus providing a framework for understanding how polyglutamine-expanded Ataxin-2 may contribute to behavioral dysregulation in neurodegenerative disease.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: F32HD112123
R01DK136479

Title: Postprandial pTOS modulates hunting and defensive behaviors through LPAG-associated circuits

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Abstract: Most mammals consume small and frequent meals. By contrast, pythons are ambush predators that exhibit extreme feeding and fasting patterns, providing a unique model to uncover molecular mediators of the postprandial response. Using untargeted metabolomics, we identified the circulating metabolite para-tyramine-O-sulfate (pTOS), which increases by more than 1,000-fold in pythons following a single meal. In pythons, pTOS production occurs in a microbiome-dependent manner via sequential decarboxylation and sulfation of dietary tyrosine. Notably, pTOS is conserved across species: it is detectable in human circulation and increases postprandially, and in both pythons and mice, pTOS administration activates a neural population in the ventromedial hypothalamus (VMH). In mice, these VMH neurons are required for the anorexigenic effects of pTOS, and chronic pTOS administration suppresses food intake and body weight in diet-induced obese mice. We further show that pTOS shapes behavioral state beyond feeding. pTOS reduces social interaction while promoting resilience to depression-like behaviors and modestly increases anxiety-like behavior while impairing cognitive performance, including novel object recognition and spatial working memory. Notably, sexual behavior remains unaffected, indicating selective modulation rather than global suppression of motivated behaviors. Together, these findings identify pTOS as a conserved metabolite that links nutrient intake to hypothalamic control of feeding and selectively reorganizes behavioral priorities, highlighting a broader role for metabolite signaling in coordinating metabolic state with brain function.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: National Natural Science Foundation of China (grant no. 82288101)

Title: Activity Dynamics and Coordination of VMHvl and pSI During the Transition from Sniffing to Attack

Authors: *J. JIANG, D. SHUMIN, Y. HU;
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Abstract: Aggression is an innate social behavior essential for survival and reproduction. However, the neural dynamics underlying the transition from social investigation, such as sniffing, to attack remain poorly understood. The ventrolateral ventromedial hypothalamus (VMHvl), which regulates sex-specific aggression, projects to the posterior substantia innominata (pSI), a region whose activation can evoke attack irrespective of sex, suggesting distinct contributions to aggressive behavior. Here, we aimed to characterize how activity and functional connectivity between VMHvl and pSI change during the transition from sniffing to attack. We performed simultaneous fiber photometry recordings of GCaMP signals from neurons in the VMHvl and pSI of singly housed male mice during resident-intruder interactions. Both regions exhibited robust activity at attack onset, with similar response magnitudes and temporal dynamics throughout attack bouts. We next compared neural activity across different sniffing contexts. During sniff-only behavior (sniffing not followed by attack), VMHvl and pSI exhibited distinct activity dynamics. In contrast, these differences were absent during pre-attack sniffing (sniffing followed by attack), when both regions displayed similar activity dynamics. To assess the functional connectivity between VMHvl and pSI, we calculated the instantaneous coefficient of determination (R^2). R^2 values during sniff-only behavior, pre-attack sniffing, and attack were all significantly elevated relative to randomly selected baseline periods. Notably, R^2 was similarly high during pre-attack sniffing and attack, but both were significantly higher than during sniff-only behavior. Together, these findings indicate that enhanced VMHvl-pSI functional connectivity emerges during pre-attack sniffing and persists throughout attack, identifying a neural correlate of the behavioral transition from social investigation to overt aggression.

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Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

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Topic: G.02. Neuroendrocrine Processes and Behavior

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FAPESP Scholarship 21/02864-9
FAPESP Scholarship 22/07530-4

Title: A ventral subiculum-lateral hypothalamic area pathway mediates spatial cue processing during social defense in mice

Authors: *A. P. ALMEIDA, A. M. TAMAIS, S. C. MOTTA;
Univ. of Sao Paulo, Sao Paulo, Brazil

Abstract: Social defense is an essential behavior that allows individual survival and group stability. As with other defensive behaviors, spatial cues (e.g. distance to the aggressor) are relevant for selecting the appropriate defensive strategy. Previously, our group showed that the juxtadorsomedial region of the lateral hypothalamic area (LHAjd) in C57BL/6 mice is recruited both by restraint stress, where the limited space is the source of stress, and social stress. In this work, we combined neural tracing, optogenetic inhibition and fiber photometry to identify a subpopulation of LHAjd neurons that receive input from the ventral subiculum (SUBv) and that is necessary for the organization of social defense, responding to spatial cues related to social defeat. Combining Fos expression and retrograde tracing, we found that LHAjd neurons receive input from SUBv neurons that are active during both restraint and social stress. Then, we used optogenetics to inhibit SUBv terminals in the LHAjd, and this manipulation disrupted social defensive behavior, leading to a decrease in time spent on fight behaviors and an impairment in the ability to orient itself towards the aggressor. Next, we performed calcium imaging using the fiber photometry approach to reveal that the activity of LHAjd neurons that receive projections from the SUBv (SUBv>LHAjd neurons) correlates with a set of defensive behaviors, such as fighting and fleeing. We also observed an increase in the signal amplitude when the aggressor is close to the recording animal. Finally, we observed that SUBv>LHAjd neurons project to different brain regions relevant for the organization of defensive behavior and stress response, such as the dorsal premammillary nucleus of the hypothalamus (PMd), lateral habenula (LHb) and lateral column of the periaqueductal gray matter (PAGl). In summary, we identified a SUBv>LHAjd pathway that integrates spatial information to organize social defensive behavior, advancing our understanding of the hypothalamic circuitry underlying the organization of defensive behavior.

Disclosures: A.P. Almeida: None. **A.M. Tamais:** None. **S.C. Motta:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.21/FF21

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Fapesp Grant #2016/18667-0
Fapesp Fellowship #2022/07530-4
Fapesp Fellowship #2024/01864-3
Fapesp Fellowship #2021/02864-9

Title: Medial amygdala activation shifts defensive behavior from passive to active coping during social trauma

Authors: *A. M. TAMAIS, A. P. ALMEIDA, S. C. MOTTA;
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Abstract: In nature, individuals repeatedly face conspecific threats to which adaptive social defense strategies are required. While innate, these behaviors are shaped by experience. In the laboratory, mice repeatedly exposed to aggressive conspecifics shift toward more passive strategy of social defense, accompanied by decreased activation of the medial amygdala (MeA). In this study, we investigated the role of the MeA and oxytocin receptor (Oxtr) signaling in shaping defensive behavior during repeated social defeat. Using the resident-intruder paradigm, C57BL/6 male mice were exposed to aggressive CD1 males for three consecutive days. Fiber photometry recordings revealed that MeA neurons were predominantly active during active defense and showed significantly decreased activation by the third day compared to the first encounter. Ubiquitous chemogenetic activation of the MeA on the third day was sufficient to shift defensive behavior back toward active coping, preventing the typical increase in passive defense and decrease in exploration observed in control animals. Using TRAP2 mice, we optogenetically activated social defeat-responsive MeA neurons on the third day, which also prevented the expected changes in defensive strategy. Additionally, we found that social defeat-responsive MeA neurons project to the sexually dimorphic hypothalamic circuit. To assess whether Oxtr signaling in the MeA is necessary for these behavioral adaptations, we knocked down Oxtr expression in the MeA. While control mice showed the expected shift toward passive defense by the third day, Oxtr knockdown mice failed to show this adaptation, maintaining active defense pattern similar to the first encounter. Together, these findings show that MeA activity and Oxtr signaling are sufficient and necessary, respectively, to modulate the shift from active to passive defensive coping during repeated social defeat. Our study uncovers a key neural mechanism underlying social defense adaptation with potential implications for understanding stress-related behavioral changes.

Disclosures: A.M. Tamais: None. **A.P. Almeida:** None. **S.C. Motta:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.22/FF22

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIDA Grant 5R01DA039062-08

Title: Modeling effects of gestational cannabis exposure on social behavior in Sprague Dawley rats

Authors: *A. PHAM[1], M. M. MCCARTHY[2], L. SIRRS[1], N. MOIN AFSHAR[1];
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Abstract: Cannabis is the most frequently used illicit drug during pregnancy, with use steadily increasing following legalization in the United States. The primary psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), is a partial agonist of the endocannabinoid (eCB) system, which is active during early neural development and integral to the proper formation of neural circuitry and subsequent behavior. Differential eCB tone in the developing posterodorsal medial amygdala (MePD) induces sex differences in rough-and-tumble play. Play is one of the earliest social behaviors expressed by individuals separate from interactions with the mom, and its robust performance during the juvenile period is highly conserved across mammalian species. We sought to determine if THC exposure would disrupt the effects of the differential eCB tone and alter sexual differentiation of the MePD and behavior. To model cannabis use during early pregnancy, we exposed Sprague Dawley rats to 5mg/kg THC in utero via subcutaneous injection to the dam from gestational days 15-21 and then investigated expression of social play during the juvenile period. Developmental THC exposure resulted in males playing less than non-exposed males and females trending towards an increase in play. Neuronal activity, determined by c-Fos expression, in the MePD was significantly higher in THC exposed females following play, and decreased in THC exposed males. With no reported sex differences in eCB receptor expression in the developing amygdala, the sex differences we saw in THC exposure led us to investigate if THC has the capability of binding other targets. We observed structural similarity between THC and testosterone and thus hypothesized that THC has the ability to bind to the sex steroid receptors. This is supported by preliminary in silico modeling as well as alterations to anogenital distance, an androgen-dependent metric, following developmental THC exposure. A current limitation to quantifying social behavior is how we quantify play, which is currently measured by an observer scoring predetermined elements (pounces, pins, boxes). We have employed machine learning to reveal latent features of play that differ at baseline between the sexes and predict they will be altered by developmental THC exposure. Social-3D Aligned Neural Network for Computational Ethology (s-DANNCE), a multi-animal pose tracking machine learning software will allow for an unbiased characterization of play. In addition to the above established findings, this approach will yield insight into the spectrum of social behavior and the effect of THC exposure on its expression.

Disclosures: A. Pham: None. **M.M. McCarthy:** None. **L. Sirrs:** None. **N. Moin Afshar:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.23/FF23

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: 5R01DA039062-08

Title: Developmental THC exposure selectively promotes adolescent social play behavior in a sex specific manner and reduces maternal aggression in a rat model

Authors: *C. V. DIONISOS, M. M. MCCARTHY, F. DAVIS, G. BROWN;
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Abstract: Cannabis use during pregnancy is rapidly increasing around the world due to expanding legalization and decriminalization. Studies of prenatal cannabis exposure in humans have focused on child behavior, but little is known about how cannabis mechanistically impacts the developing fetal brain to influence later social behavior. We use an early postnatal exposure model in rodents that mimics the third trimester of human fetal neurodevelopment to investigate the long-term socio behavioral outcomes of developmental exposure to Δ9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis. In the developing rat amygdala, males have higher endocannabinoid (ECB) levels than females, which sculpts sex specific circuitry that mediates adolescent social play, an essential prepubertal behavior that establishes proper socio-sexual adult behavior. Mimicking male-like ECB levels by treating females with THC during early neurodevelopment masculinizes social play, increasing play events to match levels observed in males. We expanded these findings by adding THC's effects on maternal behavior, maternal aggression, and empathy, a task where a rat seeks to release their cagemate from a confined chamber. In addition, we better defined the critical period in which THC exerts its effects on the aforementioned behaviors. We hypothesized that maternal behavior in particular would be negatively impacted, as there is no masculinization of maternal behavior but there was masculinized social play in the same animals. Our results show that intraperitoneal administration of THC on postnatal days 9-12, outside of the critical period for sex differentiation & amygdalar development (first postnatal week), does not increase social play in males or females as is seen from THC administration within the critical period. This effect does not persist in the empathy task as THC has no effect on this behavior regardless of when it was administered. We found no significant effects of THC on efficacy of maternal care; however we do have significance in maternal aggression- developmentally treated THC dams are less aggressive than controls. We will next probe for THC induced cellular changes in regions governing maternal behavior to help explain our behavioral effect. Our findings will help elucidate the long-term behavioral impact of developmental THC exposure to address cannabis use during pregnancy.

Disclosures: C.V. Dionisos: None. **M.M. McCarthy:** None. **F. Davis:** None. **G. Brown:** None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.24/FF24

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant 5T32GM133351-05
Salk Institute Funds
White Hall Foundation

Title: Defining the Lateral Septum Population Involved in Suppressing Aggression and its Sex Dimorphisms

Authors: *C. MARIN;
Neurobio., Univ. of California, San Diego / Salk Inst., Chula Vista, CA

Abstract: Aggression is an evolutionarily conserved behavior that is useful for survival and reproduction. However, excessive aggression is unhealthy and is a common symptom of many severe neurological disorders (e.g., post-traumatic stress disorder and dementia). Current medications treat aggression by globally dampening cognitive function rather than specifically inhibiting aggressive impulses. Compounding this problem, most neurobiological mechanistic studies on aggression are male-biased despite clear sex differences in aggression across species. These limitations underscore the need to identify endogenous neural circuits that naturally constrain aggression in both sexes. A key neural population implicated in aggression suppression is the estrogen receptor alpha-expressing population in the lateral septum (LS^{Esr1}), through suppressing the ventral lateral part of the ventromedial hypothalamus (VMHvl). Here, we interrogate the functional role of the LS^{Esr1} circuit in 8-24 week old C57BL/6J and Swiss Webster backcrossed mice of both sexes, through 1-photon miniscope imaging in freely moving mice during resident-intruder assays, along with optogenetic activation. Through this set of experiments, we reveal that the LS^{Esr1} neurons exhibit different activity patterns in the absence of a threatening conspecific compared to when a threatening conspecific enters the resident's home cage and aggression is initiated. To test whether LS^{Esr1} activity is causally involved in behavioral suppression, we complemented the imaging work with optogenetic activation. Optogenetic activation of the LS^{Esr1} population suppressed aggression, supporting a functional role for this population in tempering aggression. Together, these data identify a sex-differentiated LS^{Esr1} circuit that contributes to tempering aggression and provide functional evidence that LS^{Esr1} activity is sufficient to reduce aggressive behavior. By combining neural dynamics with causal manipulation, this work advances our understanding of how the LS is a key neural node in inhibiting aggression and establishes a framework for developing more precise, potentially sex-specific interventions for pathological aggression.

Disclosures: C. Marin: None.

Poster

PSTR367: Mechanisms and Circuits of Social and Aggresive Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR367.25/FF25

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Curci Foundation Ph.D. Scholars Program

Title: Investigating the role of basomedial amygdala neurons in social approach and anxiety

Authors: *L. TATSUMI[1,2], S. LEE[1], P. JANTARACHANATANTHITI[1], A. KUDO[1], D. W. BAYLESS[1,2];
[1]Salk Inst. for Biol. Studies, San Diego, CA; [2]Dept. of Neurobio., Univ. of California San Diego, La Jolla, CA

Abstract: Social behavior is an essential part of life in many animal species, including humans. Although the brain regions that regulate innate social behaviors, such as mating and aggression, have been studied, the neuronal populations that govern social approach, an essential step of every social interaction, are not fully understood. Additionally, sex differences underlying social approach and its mechanisms remain to be studied. Aromatase is the enzyme that catalyzes the conversion of testosterone to estrogen, and it plays a key role in brain sex differentiation and regulating social behavior. Here, we identified a previously uncharacterized population of aromatase-expressing (Aro+) neurons in the basomedial amygdala (BMA), an understudied subregion of the amygdala. We tested the function of these BMA Aro+ neurons in anxiety and social behavior and found that chemogenetic activation of these neurons in 3-5-month-old male C57BL/6 mice led to a change in approach behavior toward male mice but not toward female mice. The activation of these neurons in male mice did not lead to a significant change in anxiety-related behavior in a non-social context, suggesting a role for these neurons specifically in social contexts. Using miniscope imaging, we also monitored calcium activity of BMA neurons in freely behaving 3-5-month-old male mice, and our data revealed that these neurons respond to social conspecifics. Lastly, we discovered that the number of BMA Aro+ neurons in adult mice shows a sex difference, suggesting a potentially sex-differentiated function of these neurons in males and females. Collectively, these findings reveal an unknown function of BMA Aro+ neurons in social approach and a sex difference in those neurons.

Disclosures: L. Tatsumi: None. **S. Lee:** None. **P. Jantarachanatanthiti:** None. **A. Kudo:** None. **D.W. Bayless:** None.

Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.01/FF26

Topic: G.06. Autonomic Regulation

Support: ISF BRG grant (2751/23) (to N.S.)
Sagol Weizmann-MIT Bridge Program (2021/134368) (to N.S.)
Minerva Foundation (714146) (to N.S.)
ERA PerMed JTC2019-101 (project PerBrain)

Title: A Respiratory Pattern Biomarker in Attention Deficit Hyperactivity Disorder (ADHD)

Authors: *T. SOROKA, A. WEISSBROD, D. HONIGSTEIN, T. WEISS, N. SOBEL;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Both Attentional Deficit Hyper Activity Disorder (ADHD) and breathing patterns are associated with altered arousal and autonomic regulation, but a breathing pattern associated with ADHD has yet to be considered. In a previous study we found that humans have individual nasal airflow fingerprints. We identified members of a 97 participant cohort at a 96.8% accuracy from nasal airflow patterns alone. These fingerprints are stable in test re-test, and provides significant indications on both physiological states and cognitive traits. Here, we continuously recorded bilateral nasal airflow for 24 hours in 39 participants diagnosed with ADHD (19M, 26.6±4.07 years) and 38 matched controls (17M, 26.1±3.28 years). Among the ADHD participants, 31 completed two sessions, one on stimulant medication and one off medication. A one way ANOVA across control, on-medication, and off-medication groups revealed significant effects for Inhale duration ($F(2,105) = 4.98$, $p = 0.009$) and for the exhale pause duty cycle, the ratio of the pause coming after the exhale within the breathing cycle ($F(2,105) = 6.07$, $p = 0.003$). Both parameters were also significantly correlated with ASRS questionnaire scores (inhale duration, $R = -0.30$, $p = 0.0107$ and exhale pause duty cycle, $R = 0.29$ $p = 0.013$). Classification by breathing alone between the control and the off-medication groups reached 79.22% accuracy. Classification between on and off medication groups yielded 96.77% accuracy. In other words, we correctly labeled 30 of 31 participants. Further studies will explore the causality of this relationship; whether individuals breathe differently because they have ADHD, or whether differences in respiratory patterns may predispose individuals towards ADHD.

Disclosures: T. Soroka: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The Weizmann Institute of Science has applied, in the names of all authors, patent on diagnosing ADHD from patterns of nasal airflow. **A. Weissbrod:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The Weizmann Institute of Science has applied, in the names of all authors, patent on diagnosing ADHD from patterns of nasal airflow. **D. Honigstein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The Weizmann Institute of Science has applied, in the names of all authors, patent on diagnosing ADHD from patterns of nasal airflow. **T. Weiss:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The Weizmann Institute of Science has applied, in the names of all authors, patent on diagnosing ADHD from patterns of nasal airflow. **N. Sobel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); hold also a patent for the measurement device.

Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.02/FF27

Topic: G.06. Autonomic Regulation

Support: JST PRESTO JPMJPR21S4
JST SPRING JPMJSP2124

Title: Within-concert reproducibility of respiratory dynamics in a professional string quartet

Authors: *Y. HATTORI[1], R. NISHIZONO[2], K. HONDA[2], K. KOMAZAKI[2], G. SATO[2], H. MIWA[3], T. NAKAYAMA[3], H. HASEGAWA[3], S. FUJII[5], T. I. SHIRAMATSU[6], K. KONDO[6], N. SAIJO[2], J. KUNIMATSU[4];
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Abstract: Respiration is shaped by metabolic demand, but also by motor demand and cognitive state including attention and arousal. Expert musical performance requires precise control of ongoing movement and sustained regulation of task-related cognitive state, possibly yielding highly reproducible respiratory dynamics. We therefore conducted an exploratory analysis to examine whether respiratory dynamics show reproducible structure within a concert and whether this structure is preserved across concerts that differed in audience context.
We recorded respiration from the four male members of a professional string quartet during two concert sessions of the same program that differed in audience presence, thereby altering the cognitive and social context while preserving the musical material. Respiratory time series were recorded using nasal temperature sensors and aligned to the musical structure. We quantified respiratory reproducibility within each performer in two ways. Within-concert reproducibility was defined as the correlation between respiratory trajectories for repeated occurrences of the same passage within a concert, whereas between-concert reproducibility was defined as the correlation between respiratory trajectories for corresponding passages across the two concert sessions.
Across both performances, respiration showed reliable within-concert reproducibility: repeated sections within the same concert elicited similar respiratory trajectories within individual performers (mean ± SD: $r = 0.442 \pm 0.200$, $n = 24$ passage-performer pairs). In contrast, corresponding sections across concerts did not show comparable reproducibility (mean ± SD: $r = -0.007 \pm 0.100$, $n = 24$ passage-performer pairs). Thus, respiratory dynamics were not fixed solely by the practiced motor sequence, but varied across performance occasions, potentially reflecting changes in performers' cognitive state across the experimentally varied contexts. Importantly, however, respiration remained reproducibly organized within each concert despite this context-dependent variability.
Our study suggests that respiration during expert performance contains reproducible within-concert structure while being sensitive to performance context.

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Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.03/FF28

Topic: G.06. Autonomic Regulation

Support: NINDS R01 NS133139

Title: Postictal Central CO_2 Chemoreception is Not Dependent on Cyclooxygenase-2 Activity in a Scn8a Epilepsy Mouse Model

Authors: *T. K. MARC[1], M. L. SCULIMBRENE[2], I. C. WENKER[3];
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Abstract: Sudden unexpected death in epilepsy (SUDEP) is defined as the sudden and unexpected death with unknown cause of a person with epilepsy (PWE). PWE that have uncontrolled seizures, high seizure frequency, and generalized tonic-clonic seizures have higher risk of SUDEP. Clinical data suggests that apnea is the primary cause of death following seizures. Results from our lab and others found that epilepsy mouse models have seizure-induced apnea leading to death. However, the physiological mechanism that causes this failure of breathing is unknown.The most significant drive to breathe is central CO_2 chemoreception, where specialized brainstem neurons detect tissue CO_2 levels to regulate breathing. Clinical and preclinical evidence indicates that hypercapnic ventilatory response (HCVR), a measure of CO_2 chemoreception, decreases postictally. Work from our lab measuring response to CO_2 before and after inducing audiogenic seizures showed that HCVR decreased postictally. The mechanisms to prevent reduced HCVR postictally have yet to be investigated. In other epilepsy rodent models, treatment with cyclooxygenase-2 inhibitor (COX-2) ibuprofen prior to inducing seizures suppressed cerebral arteriole dilation, prevented postictal hypoxia, and SUDEP. Thus, we hypothesize that suppression of CO_2 chemoreception after seizures is also COX-2 dependent. In this study, we examine the preictal and postictal HCVR with and without dose of ibuprofen(100 mg/kg) in an epilepsy model with N1768D mutation in an *Scn8a* allele (D/+ mice). 8-week-old D/+ mice were implanted with telemetric probes to record core body temperature. After recovery from surgery, whole-body plethysmography was used to record breathing parameters. The mice were habituated to experimental chamber, and HCVR was tested by measuring respiratory parameters at 0%, 3%, and 6% inspired CO_2. Next, through intraperitoneal injection, D/+ mice were given DMSO or 100 mg/kg of ibuprofen. After 30 minutes, 4 audiogenic seizures were evoked (15 kHz pure tone at 80 dB), each 5 minutes apart, and then the HCVR was tested 5 and 20 minutes postictally. No significant difference was observed between DMSO controls and ibuprofen treated groups (Mann-Whitney, $p = 0.8857$). Additionally, no significant difference was observed between HCVR before and after ibuprofen injection at 5 minutes (1-way ANOVA, $p = 0.0982$) and 20 minutes postictally (1-way ANOVA, $p =0.1118$). This suggests that dilating blood vessels alone does not improve HCVR. Further research on CO_2 sensing mechanisms in the brainstem is needed to understand why HCVR is reduced after seizures, in hopes of developing targeted therapies for SUDEP.

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Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

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Program #/Poster #: PSTR368.04/FF29

Topic: G.06. Autonomic Regulation

Support: R01HL128970
R01HL174409

Title: Dual GLP-1/GIP agonist, tirzepatide, increases hypercapnic ventilatory response in diet-induced obese mice

Authors: *M. ALEXIS RUIZ[1], N. WILLIAMS[2], M. R. AMORIM[3], V. POLOTSKY[4];
[1]Anesthesiol. and Critical Care, The George Washington Univ. Sch. of Med. and Hlth. Sci., Washington, DC; [2]Anesthesiol. and Critical Care Med., The George Washington Univ., Woodbridge, VA; [3]Anesthesiol. and Critical Care, The George Washington Univ., Washington, DC; [4]Anesthesiol. and Critical Care, George Washington Univ., Washington, DC

Abstract: Background: Obesity hypoventilation syndrome, the most severe form of sleep disordered breathing (SDB), is manifested by daytime hypercapnia due to a defect in the hypercapnic ventilatory response (HCVR). Glucagon-like peptide receptor-1 agonists tirzepatide induce weight loss and treat SDB in obese patients, but whether their therapeutic effect on SDB is entirely due to weight loss or there is an independent effect on control of breathing. Objective: To examine the effect of tirzepatide, on baseline breathing and the HCVR in C57BL/6J male mice with diet induced obesity (DIO) and determine if this effect is independent of metabolism. Methods: C57BL6 male mice with DIO (n=8) underwent acute (single 10 nmol/kg tirzepatide subcutaneous dose) and chronic (10nmol/kg daily for 7 days) crossover treatment protocols in a random order. Mice underwent a two-week washout period before the crossover. Minute ventilation (VE) was measured during quiet wakefulness at normocapnia and 8% CO_2 in a thermoneutral environment (28-30°C) after each treatment. HCVR was calculated as the slope of VE versus inspired CO_2 using linear least-squares regression. Metabolic studies (oxygen consumption, VO2, and CO2 production, VCO2) were performed on Day 1 and Day 7 in the thermoneutral environment with the same acute and chronic protocols using the SABLE Systems unit. Results: After a single dose of tirzepatide, normocapnic ventilation did not change, whereas hypercapnic VE increased due to increase tidal volume from 0.46 to 0.52 (mL/breath). VCO2 decreased significantly without a change in VO2, reducing respiratory exchange ratio (RER, 0.82 to 0.75) indicating a switch to utilization of fat. After 7 days, tirzepatide increased normocapnic and hypercapnic VE and the HCVR. Hypercapnic VE increased from 3.58 to 5.71 (mL/min/g), and HCVR increased from 0.34 to 0.52 (Δml/min/Δ%CO2/g). However, these changes occurred with marked weight loss and hypermetabolism with VCO2 increasing from (light phase: 1194 to 1771; dark phase: 1488 to 1862 mL/kg/h) and VO2 increasing from (light phase: 1464 to 2427; dark phase: 1807 to 2568 mL/kg/h). RER continued to decrease due to fat oxidation. Conclusions: Acute and chronic tirzepatide treatment shifted metabolism to burning fat and

increased hypercapnic sensitivity. An increase in hypercapnic VE after a single dose of tirzepatide was independent of metabolism, since VCO2 was decreased. Chronic tirzepatide increased baseline and hypercapnic VE and HCVR in the settings of weight loss and hypermetabolism with increased utilization of fat. We were unable to determine if the respiratory effects of 7-day tirzepatide treatment were independent of metabolism.

Disclosures: M. Alexis Ruiz: None. **N. Williams:** None. **M.R. Amorim:** None. **V. Polotsky:** None.

Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.05/FF30

Topic: G.06. Autonomic Regulation

Support: FAPESP Grant 2025/03660-9
FAPESP Grant 2025/05255-4

Title: Pre-Bötzinger complex activation suppresses active expiratory pattern

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Abstract: Rhythmic contractions of abdominal muscles, or active expiration (AE), emerge in conditions of increased respiratory drive, including hypercapnia and hypoxia, due to the activation of expiratory neurons in the lateral parafacial respiratory group (pFL). Previous studies suggest that neurons of the pre-Bötzinger complex (preBötC), the primary inspiratory rhythm generator, are connected to the pFL and coordinate the formation of the AE motor pattern. However, the functional role of preBötC-to-pFL pathways remains unclear. Here, we explored the hypothesis that the preBötC neurons restrain the emergence of the AE pattern. Experiments were performed in in situ working heart-brainstem preparation from juvenile male Sprague-Dawley Holtzman rats. Respiratory motor outputs were monitored through recordings of phrenic (PN), cervical vagus (cVN), and abdominal (AbN) nerves during baseline (5% CO2) and hypercapnic (10% CO2) conditions. The preBötC neurons were activated unilaterally with glutamate (10 mM) or substance P (10 μM) or partially inhibited with isoguvacine (GABAA receptor agonist, 10 mM) microinjections. All procedures were approved by the Animal Ethics Committee of Sao Paulo State University (Protocol No. 17/2020). Glutamate and substance P microinjections into the pre-BötC significantly increased PN burst frequency ($P < 0.006$, n=7-8) in all experimental conditions and suppressed hypercapnia-induced expiratory AbN activity (glutamate: 40,0 ± 23,1 vs 7,7 ± 8,9 μV; substance P: 46,8 ± 21,4 vs 22,7 ± 21,4 μV, $P < 0,005$, n=7). In contrast, the partial inhibition of the preBötC with isoguvacine reduced PN and cVN activity amplitude ($P < 0.04$, n=6), and increased the duration of AbN expiratory bursts during hypercapnia (1,2 ± 0,51 vs 1,7 ± 0,59 s; $P = 0,0002$, n=5). Our findings demonstrate that

activation of preBötC inspiratory neurons inhibits the expression of AE pattern, indicating that the inspiratory oscillator exerts a potent functional inhibitory control over expiratory networks.

Disclosures: I.P. Leirão: None. **D.B. Zoccal:** None.

Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

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Topic: G.06. Autonomic Regulation

Support: São Paulo Research Foundation (FAPESP)
National Council for Scientific and Technological Development (CNPq)

Title: Phase-dependent modulation of breathing by inhibitory somatostatinergic interneurons of the lateral parafacial region from mice

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Abstract: The parafacial region (pFL) contains somatostatinergic (Sst) interneurons, but their role controlling pulmonary ventilation remains unclear. We used genetically modified mice expressing Cre in Sst neurons. Cre- and FLP-dependent viruses were coinjected into the pFL to express channelrhodopsin (ChR2) in Sst interneurons. An optical fiber was implanted for light delivery. We measured respiratory frequency (fR), tidal volume (VT), pulmonary ventilation (VE), and the duration of the respiratory cycle, inspiration (DI), and expiration (DE) during normocapnia and hypercapnia (7% CO2) in unanesthetized mice. A 473 nm laser (10 mW) was used to activate Sst interneurons using short pulses (0.05, 0.1, and 0.2 s at 0.05 Hz), applied during the inspiratory and expiratory phases, and long pulses (5, 20, and 60 s at 20 Hz). Sst-Flp, Vgat-Cre, Ai65F, and Ai6 mice were also crossed to express GFP in inhibitory neurons and td-Tomato in Sst neurons. Paired and unpaired Student's t-tests were used. Optogenetic activation of pFL Sst interneurons during 5s (n=8), 20s (n=6), and 60s (n=6) increased fR (p=0.008; p=0.01; p=0.02), VT (p=0.0002; p=0.001; p=0.0006) and VE (p=0.001; p=0.005; p=0.005), but decreased respiratory cycle duration (p=0.001; p=0.009; p=0.006) and DI (p=0.007; p=0.004; p=0.005), without affecting DE during normocapnia. Similar responses occurred during hypercapnia using the 5s protocol (n=6) (fR:p=0.01; VT:p=0.01; VE:p=0.006; duration of the respiratory cycle:p=0.02; DI:p=0.008). The 20s protocol (n=6) increased VT (p=0.03), VE (p=0.03) and decreased DI (p=0.03), while the 60s protocol (n=6) affected only DI (p=0.03). Optical activation for 0.05s (n=6) during the inspiratory phase reduced respiratory cycle duration (p = 0.03), DI (p = 0.03), and DE (p = 0.008), without affecting VT. No changes were observed when optical activation occurred during expiration. For 0.1 s, there was a reduction in respiratory cycle duration when optical activation occurred during inspiration (n=8) (p = 0.04) and expiration (n=9) (p = 0.003), with no changes in VT, DI or DE. For 0.2 s optical activation

during the inspiratory phase (n=6), there was an increase in VT ($p = 0.03$) and a reduction in respiratory cycle duration ($p = 0.001$) and DE ($p = 0.02$), with no change in DI. No changes were observed when optical activation occurred during expiration (n=7). We also found that all Sst-positive neurons in pFL are inhibitory (n=4). We conclude that the activation of inhibitory pFL Sst interneurons increases ventilatory parameters during normocapnia and hypercapnia, and modulates breathing in a phase- and duration-dependent manner, predominantly affecting inspiration.

Disclosures: N. Salim: None. **R. Martins Sá:** None. **D.J. Moraes:** None.

Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.08/GG1

Topic: G.06. Autonomic Regulation

Support: NIH R01/HL133100

Title: Carotid body Trpm7 deletion attenuates leptin-dependent chemoreflex sensitization induced by intermittent hypoxia.

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Abstract: Carotid body Trpm7 deletion attenuates leptin-dependent chemoreflex sensitization induced by intermittent hypoxia.Background: Intermittent hypoxia (IH), a hallmark of sleep apnea, sensitizes the carotid body (CB), increasing carotid sinus nerve (CSN) activity, hypoxic chemoreflexes, and sympathetic drive. We previously showed that IH increases plasma leptin levels and leptin enhances CSN activity in obesity through upregulation of CB Trpm7. Preliminary data indicate that IH increases leptin receptor ($Lepr^b$) and Trpm7 gene expressions in CB type I glomus cells.**Hypothesis:** IH increases baseline CSN activity and CB hypoxic chemoreflex sensitivity through leptin-Trpm7 signaling, and these effects are attenuated by Trpm7 knockout in CB glomus cells.**Methods:** Trpm7 flox control mice (N=12) and Trpm7 flox × ThCre mice with Trpm7 knockout in tyrosine hydroxylase-positive cells, including CB glomus cells (N=12), were exposed to either IH (21% to 6% O_2, 60 cycles/hr for 5 days; n=6/strain) or room air (RA; N=6/strain). CB bifurcations were isolated for ex vivo CSN recordings under normoxic (PO_2=100 Torr) and hypoxic (PO_2=60 Torr) conditions in the absence or presence of leptin (50 nM) and the Trpm7 inhibitor FTY720 (3 mM). Two-way repeated-measures ANOVA assessed effects of IH, leptin, and their interaction on baseline CSN activity and hypoxia-evoked responses [$\Delta(Hx-Nx)$].**Results:** In Trpm7 flox controls, IH significantly increased baseline CSN activity ($P<0.001$). Leptin further enhanced CSN activity under both RA and IH, with a greater effect after IH exposure (interaction $P<0.001$). FTY720 attenuated leptin-

induced excitation. Similar effects were observed for hypoxia-evoked responses, with significant effects of IH (P=0.009), leptin (P<0.001), and their interaction (P=0.012). In Trpm7 flox × ThCre mice, IH and leptin had no significant effects on baseline CSN activity. IH still enhanced hypoxic chemoreflex responses (P=0.007), but leptin and FTY720 produced no additional effects.**Conclusions:** IH augments baseline CSN activity through leptin-Trpm7 signaling. Leptin amplifies IH-induced CB hypoxic chemoreflex sensitization via a Trpm7-dependent mechanism. Targeting the leptin-Trpm7 axis may reduce CB-driven sympathetic excitation in sleep apnea and metabolic cardiovascular disease. Supported by NIH R01 HL133100.

Disclosures: A. Roy: None. **M. Shin:** None. **V. Polotsky:** None.

Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR368.09/GG2

Topic: G.06. Autonomic Regulation

Support: NIH Grant 5672830
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Title: Orexin neurons are not activated by CO_2/H^+ or hypoxia in brain slices maintained under high glucose conditions

Authors: *E. NUNES DA SILVA[1], T. A. JANES[2], R. KINKEAD[3], V. SILVA OLIVEIRA[4], M. B. DIAS[5], D. K. MULKEY[6];
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Abstract: Orexin neurons are not activated by CO2/H^+ or hypoxia in brain slices maintained underlow metabolic stress conditions of high O2 and high glucose. Orexin neurons modulate arousal, metabolism, and respiratory function, and evidence suggeststhat these neurons may function as respiratory chemoreceptors. At the cellular level, they havebeen shown to respond to acidification under low O2 and glucose (1 mM) conditions. However, itremains unclear whether this response is retained under experimental conditions designed to limitmetabolic stress (e.g., high glucose and high O2). Furthermore, sensitivity of orexin neurons tohypoxia is not well characterized. To test these possibilities, we recorded from orexin neurons inhypothalamic slices from orexin-eGFP mice or rats injected with AAV2/9-promHCRTeGFP tolabel orexin neurons. Cell-attached and whole-cell patch-clamp recordings were used to evaluateneuronal responses to hypercapnia (10% CO2) against a balance of O2 (high O2) or N2 (low O2).We found that orexin neurons showed negligible firing responses to elevated CO_2/H^+ in

either miceor rats, regardless of background O2 levels. Similarly, exposure to extracellular acidification inbicarbonate-free HEPES-buffered solution did not affect activity of orexin neuron. We did find asubset of orexin neurons reversibly inhibited by hypoxia by activation of a weakly rectifyingconductance K^+ conductance. These results show that orexin neurons are not intrinsically sensitiveto CO_2/H^+ under typical brain slice conditions of high glucose. Based on previous evidence thatorexin neurons are activated by $CO2/H^+$ under low glucose conditions, we speculate orexin neuronsfunction as conditional respiratory chemoreceptors where $CO2/H^+$ sensitivity is dependent on thelocal metabolic state.

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Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

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Program #/Poster #: PSTR368.10/GG3

Topic: G.06. Autonomic Regulation

Support: NIH Grant U01NS090414
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NIH Grant R01NS123155

Title: Real-time serotonin levels in the medulla during hypercapnic challenges

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Abstract: Serotonergic neurons play an important role in central chemo sensation and respiratory homeostasis; however, the real-time dynamics of serotonin signaling during hypercapnia remain poorly understood. Here, we used fiber photometry in combination with the serotonin sensor GRAB_g5-HT3.0 to quantify serotonin dynamics within the ventrolateral medulla (VLM), which contains respiratory neurons, during hypercapnic challenges in mice. Adult mice received stereotactic injections of pAAV-hSyn-GRAB_g5-HT3.0 into the VLM, followed by implantation of a 400 μm fiber optical cannula for *in vivo* recordings. Two to four weeks after implantation, which allowed for sensor expression, real-time serotonin release was recorded during exposure to graded hypercapnia (0%, 5%, and 10% CO_2 in 50% O_2) and hypoxia (10% O_2) while mice were placed in a head-out plethysmography chamber. Hypercapnic exposure produced robust, dose-dependent increases in serotonin-associated fluorescence signals in a subset of mice, with greater responses observed during 10% CO_2 compared to 5% CO_2; additionally, hypoxic exposures produced the opposite response. To validate sensor expression

and ability to detect increased serotonin levels, a separate cohort of mice received intraperitoneal injections of MDMA (28mg/kg dose), which produced large increases in fluorescence following systemic administration. Injection of the selective serotonin reuptake inhibitor (SSRI) paroxetine also enhanced serotonin signaling, with even larger responses observed in response to CO_2, further validating the observed dynamics. Together, these findings provide direct *in vivo* evidence that serotonin signaling within the VLM dynamically tracks hypercapnia load, supporting an active role for serotonin neurons in respiratory homeostasis and central CO_2 chemoreception. This work highlights the importance of serotonergic mechanisms in respiratory regulation and provides insight into disorders associated with impaired respiratory control.

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Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.11/GG4

Topic: G.06. Autonomic Regulation

Support: NIH grant U01 NS090414

Title: pH chemosensitivity of medullary raphe serotonin neurons is mediated by a calcium activated nonselective cation current.

Authors: Y. WU[1], E. BRAVO[2], ***G. B. RICHERSON**[2];
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Abstract: A subset of serotonin neurons (5-HT) in the medullary raphe have emerged as prominent candidates for central respiratory chemoreceptors, and have a number of specialized properties that would help them perform that role. Recently, these neurons were found to have a high degree of intrinsic chemosensitivity after acute dissociation. Here we report that these neurons express a novel ion current with an unusually high degree of sensitivity to small changes in pH. The medullary raphe was dissected from the brainstem of P1-P2 mice that expressed EYFP under control of the enhancer region of ePet, labeling 5-HT neurons. Neurons were dissociated and plated on glass coverslips and grown for at least 12 days *in vitro* (DIV) to allow maturation of chemosensitivity. Patch clamp recordings from EYFP+ neurons identified that depolarization from -50 to +70 mV activated an outward current that slowly deactivated upon return to -130 mV. This tail current had a steep dependence on pH, being maximally active at pH 7.6 and completely inhibited at pH 7.0. In individual neurons the level of expression of the tail current in voltage clamp strongly correlated with the change of firing rate in response to pH in current clamp. The tail current was eliminated by removal of calcium from the extracellular solution or substitution with 200 uM cadmium. A voltage-clamp depolarizing ramp protocol led to activation of an outward rectifying current. This rectification was linearized by adding calcium

to the pipette solution or by causing release of calcium from intracellular stores with PIP_2 (10 uM) added to the pipette solution. Under conditions where the Nernst potential for K+ -98 mV, the reversal potential of the pH sensitive current was -71 mV. Ion substitution experiments revealed that the pH sensitive current was permeable to both K+ and Na+, in a ratio of 7:1. The change in firing rate in response to acidosis and the pH sensitive current were not blocked by apamin (500 nM) or charybdotoxin (200 nM). The change in firing rate in response to acidosis was not blocked by PPADS (100 uM) or methanandamide (10 uM). The pH sensitive current was blocked by flufenamic acid (100 uM). We conclude that the high degree of chemosensitivity of a subset of medullary 5-HT neurons is mediated by a novel calcium-activated nonselective cation current with an unusually high permeability to Na+.

Disclosures: Y. Wu: None. **E. Bravo:** None. **G.B. Richerson:** None.

Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.12/GG5

Topic: G.06. Autonomic Regulation

Support: NIH grant UG3DA062506

Title: Oxytocin maintains and augments fentanyl-induced analgesia in a chronic pain model in rats

Authors: *D. JAIN[1], D. S. MENDELOWITZ[2], J. ESCOBAR[3], M. NIKULINA[4];
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Abstract: Opioid use for chronic pain management remains widespread but has serious adverse risks, including respiratory depression and mortality. Opioid antagonists such as naloxone can reverse respiratory depression but naloxone use reverses analgesia and can cause withdrawal, complicating effective pain treatment. Identifying alternative therapies that maintain or enhance opioid analgesia while decreasing the incidence of respiratory depression is therefore of significant clinical importance. Our prior work (PMID: 42208348) showed oxytocin (OXT) can treat fentanyl induced respiratory depression. This study tested the hypothesis that oxytocin can preserve or improve fentanyl-induced analgesia in rats in a Chronic Constriction Injury (CCI) model of chronic neuropathic pain. Nociceptive thresholds were assessed using the Hargreaves thermal assay after administration of fentanyl, fentanyl+naloxone, or fentanyl+OXT. Fentanyl produced a marked increase in withdrawal latency, indicating analgesia. Naloxone reversed this effect. In contrast, oxytocin did not blunt, and improved, fentanyl's analgesic action. These findings indicate that, unlike traditional opioid antagonists, oxytocin preserves and may potentiate opioid-mediated analgesia while also reversing opioid induced respiratory depression. Given its established safety profile, oxytocin represents a promising therapeutic opportunity for

reducing respiratory depression while improving analgesia with the use of opioids in chronic pain management.

Disclosures: D. Jain: None. **D.S. Mendelowitz:** None. **J. Escobar:** None.

Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

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Program #/Poster #: PSTR368.13/GG6

Topic: G.06. Autonomic Regulation

Support: HHS/NIH/National Institutes of Health 1UG3DA062506

Title: Benefits of PVN oxytocin neurons activation on OSA patients

Authors: *X. WANG[1], V. JAIN[2], G. CRESSWELL[3], J. ESCOBAR[1], N. H. LEE[1], D. S. MENDELOWITZ[1];
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Abstract: The primary cause of obstructive sleep apnea (OSA) is the partial or complete collapse of the upper airway. Consequently, patients experience intermittent hypoxia and hypercapnia. If left untreated, OSA can trigger low grade systemic inflammation and severe cardiovascular complications. Research utilizing wearable devices and polysomnography has consistently reported OSA includes a reduced stage III NREM deep sleep, repeated arousals, daytime somnolence, fatigue, and cardiovascular pathologies including hypertension and increased risk of myocardial infarction. Previous investigations from our lab demonstrated that the activation of oxytocin neurons in the paraventricular nucleus of the hypothalamus (PVN) improves cardiovascular and respiratory function in chronic intermittent hypoxia (CIH), and hypercapnia (CIHH), heart failure and myocardial ischemia rodent disease models. Neurons essential for cardiac and respiratory function exhibit dense oxytocinergic innervation and high expression of oxytocin receptors. Furthermore, selective activation of presynaptic terminals on the dorsal motor nucleus of vagus and the hypoglossal nucleus using chemogenetic and optogenetic techniques enhances the activation of cardiac vagal neurons and hypoglossal motoneurons, respectively. Our prior studies in patients with OSA have shown administration of intranasal oxytocin decreases duration of apneas and hypopneas and increases respiration rate. Our current ongoing project examines, in a randomized double-blind crossover placebo-controlled trial, if two weeks of intranasal oxytocin administration improves systemic biomarkers of inflammation in OSA patients.

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Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.14/GG7

Topic: G.06. Autonomic Regulation

Support: Kuni Foundation Grant 1030372

Title: Feasibility of Inducing a Torpor-Like State in a Rat Model of Glioblastoma to Support the Development of Hypothermia-Based Cancer Treatments

Authors: *S. HOLLAND[1], J. F. YUNG[1], L. MULDOON[1], D. TUPONE[2], M. WOOD[1], R. BARAJAS[1];
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Abstract: Torpor-like state (TLS), characterized by reductions in core body temperature (T_{CORE}), metabolic rate, and immune activity as occurring in natural torpor, has been proposed as a strategy to enhance cancer treatment and mitigate chemo-radiotherapy toxicity. While TLS can be safely induced in healthy non-hibernating mammals via central A1 adenosine receptor activation, its feasibility in brain tumor models with tumor-associated neural circuitry disruptions remains unknown. To determine if the presence of intracerebral tumor impaired the induction and depth of the TLS-associated hypothermic state, forty Long-Evans rats (200-300 g) anesthetized with isoflurane in O_2, were implanted with an intracerebroventricular cannula for administration of a TLS-inducing agent, a rat glioma-2 allograft in the right caudate nucleus, and an intraperitoneal telemetric temperature probe for continuous monitoring of T_{CORE}. Following recovery from tumor allograft implantation, TLS was induced on either Day 3 or Day 8, with tumor progression monitored by magnetic resonance imaging (MRI) at the same time points. TLS was also induced in a separate group of healthy control rats to enable comparison of T_{CORE} at baseline and at the nadir of the hypothermic response with that of tumor-bearing animals. T1-weighted Gadolinium-enhanced MRI scans were analyzed to determine tumor volume using Horos software. We found that TLS could be consistently induced in tumor-bearing animals at both early and advanced stages of tumor growth. Tumor volume increased significantly between Day 3 and Day 8 after implantation (Day 3: 17.3 ± 8.7 mm³; Day 8: 59.8 ± 8.7 mm³; t-test, $p < 0.001$). Despite this progression, the depth of TLS-induced hypothermia was comparable between the two groups, with T_{CORE} reaching 25.1 ± 0.3°C on Day 3 and 24.9 ± 0.9°C on Day 8 (t-test, $p = 0.9$). Furthermore, the magnitude of hypothermia achieved in tumor-bearing animals was not significantly different from that observed in age-matched naïve controls (T_{CORE} decrease at 26.7 ± 0.8°C), indicating that the presence of the intracranial tumor did not impair the induction or depth of the TLS response. These findings demonstrate that TLS can be reliably induced and tolerated in rats bearing intracranial glioma allografts, despite substantial tumor progression. Tumor presence did not alter the induction or depth of the TLS-associated hypothermic response, establishing the feasibility of applying TLS in experimental brain tumor models. This work provides the foundation for the implementation of experimental TLS in brain tumor models for future investigations of TLS as an adjunctive strategy for glioblastoma treatment.

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Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

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Program #/Poster #: PSTR368.15/GG8

Topic: G.06. Autonomic Regulation

Support: R01 MH131317

Title: Effect of metabolic state on the electrophysiological properties of hypothalamic neurons

Authors: *C. SILVA RUBIO[1], F. VAN BREUKELEN[2], D. H. BRAGER[2];
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Abstract: All mammals possess thermoregulatory strategies that are influenced by their respective past and present environments. A striking example can be found in mammals that engage in torpor, a metabolically reduced state that results in a lowered body temperature that is sustained for less than a day to several months. Thermoregulatory mechanisms require environmental temperature to be continuously detected by the nervous system. Feedforward and feedback temperature signals converge within the preoptic area (POA) of the hypothalamus to elicit the appropriate effector responses. Previous studies investigating the electrophysiological properties of POA neurons focus on mice and rats, mammals that constantly maintain a body temperature of 37°C, limiting an overall understanding of POA neurons in mammals that are not homeothermic. This observation brings into question the electrophysiological differences that may exist in POA neurons between homeothermic and heterothermic mammals. We therefore set out to measure the electrophysiological properties of POA neurons in acute brain slices from the following species that vary in thermoregulation: laboratory mice (*Mus musculus*), ground squirrels (*Callospermophilus lateralis*), opossums (*Monodelphis domestica*) and tenrecs (*Tenrec ecaudatus*). Species comparisons when animals were active resulted in no differences in steady-state input resistance, membrane time constant, or AP threshold, peak, and afterhyperpolarization. Opossum neurons had a more depolarized resting membrane potential (V_m) compared to the other 3 species. Active and torpid metabolic states were compared only in ground squirrels where torpid neurons had a higher spontaneous firing frequency, a more depolarized resting V_m, and AP threshold values compared to active neurons. We are currently testing the hypothesis that these differences are due to torpor by measuring the properties of POA neurons in fasting-induced torpid mice. These experiments will provide a framework to investigate the neuronal basis of thermoregulation and temperature homeostasis across all mammals.

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Poster

PSTR368: Respiratory, Thermal, and Metabolic Regulation

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Title: Preoptic Neurons that Control Entry into Hibernation

Authors: *A. J. MARTINEZ[1,3], C. M. REID[3], A. J. LAVIN-PETER[3], W. LI[3], A. S. LEE[3], E. C. GRIFFITH[4], S. HRVATIN[3,2,5];
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Abstract: Evolution of seasonal hibernation has enabled mammals to survive harsh conditions by entering a state of prolonged hypometabolism and hypothermia with body temperatures as low as 0-4°C. Despite decades of physiological studies, the genetic tools to study hibernation have remained limited and the mechanisms that induce hibernation entry are still unknown. Focusing on the brain, we map state-dependent neuronal activity across the hibernation cycle in Syrian hamsters and identify the hypothalamic anterior preoptic area (aPOA) as a key regulator of hibernation entry. Single-nucleus RNA and chromatin profiling provided a map of neuronal populations present in the hamster POA and enabled the discovery and design of an enhancer AAV that selectively targets hibernation-associated aPOA subpopulations. Using this genetic approach, we show that *Samd3*-positive aPOA glutamatergic neurons are necessary for entry into hibernation and that their activation is sufficient to induce a prolonged hypothermic state with associated nesting behavior. Together, we identify the first neuronal population that controls entry into hibernation, opening new avenues for investigating and manipulating the metabolic and physiological mechanisms underlying this extreme state of “suspended animation” and its potential applications in aging and disease.

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Poster

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Program #/Poster #: PSTR368.17/GG10

Topic: G.06. Autonomic Regulation

Support: NIH DP1-AT011979-01

Title: Mapping the brain-body interactome through sympathetic taxonomy and circuitry

Authors: *Z. LEWIS[1], L. REMÉDIO[1], K. FANCHER[1], C. M. WEBER[1], A. VICENTE[1], T. FINNEMORE[1], E. THOMAS[1], S. YAO[1], K. SMITH[1], D. BERTAGNOLLI[1], A. CHAKKA[1], R. FERRER[1], J. GOLDY[1], J. GUZMAN[1], K. JAMES[1], B. NGUY[1], T. CARDENAS[1], C. RIMORIN[1], D. B. ROCHA[1], M. TIEU[1], A. TORKELSON[1], D. S. PETERKA[2], H. ZENG[1], B. TASIC[1], R. M. COSTA[1];
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Abstract: Core biological functions depend on close integration between the brain and peripheral organs. Traditionally, the sympathetic nervous system is known to broadcast states of stress for the “fight or flight” response, but it is increasingly recognized as a hub of brain-body communication that can precisely and independently regulate physiological responses such as heart rate, digestion and immune response. We report initial results towards an effort to construct a “brain-body interactome” focusing on the sympathetic nervous system. We used single-nucleus RNA-sequencing, single-nucleus epigenomics, retrograde labeling, and integration with published single-cell atlases to generate a preliminary transcriptomic taxonomy spanning most sympathetic ganglia. This analysis reveals distinct transcriptomic cell types that fall into broad functional classes, including cardiovascular and digestive (“fight or flight”) neurons, secretomotor neurons, and non-adrenergic neurons such as cholinergic sudomotor cells. We also investigated the pre- and postsynaptic pathways of ganglionic sympathetic neurons. To identify presynaptic sympathetic circuits innervating the Celiac-Mesenteric Ganglia (CMG), we used monosynaptic retrograde labeling with rabies virus. Surprisingly, we identified not only brainstem and hypothalamic neurons but also corticospinal neurons projecting directly to preganglionic, CMG-innervating spinal cord neurons. To identify postsynaptic circuits from the CMG, we retrogradely traced neurons innervating the spleen and pancreas and found that individual neurons in the CMG typically innervate one organ or the other, and a small percentage of these innervate both. We are utilizing the transcriptomic taxonomy of CMG neurons to identify molecularly-defined populations innervating the spleen and pancreas. Together, these results establish a cellular taxonomy of the sympathetic nervous system and provide a foundation for developing a viral genetic toolkit and a connectivity map of the sympathetic nervous system. With this "brain-body interactome,” we aim to enable precise manipulation of different brain-body pathways to advance basic research and new treatments for autonomic disorders.

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Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.01/GG11

Topic: G.07. Biological Rhythms and Sleep

Support: Pritzker Neuropsychiatric Disorders Research Consortium

Title: Infraslow respiratory rate fluctuations during REM sleep are associated with neuropsychiatric symptoms in humans

Authors: *L. S. BUENO-JUNIOR[1], P. T. WICKHAM[2,3], C. J. TINSLEY[2,3], M. M. LIM[2,3], B. O. WATSON[1];
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Abstract: Respiratory rate variations during human REM sleep have traditionally been considered “irregular”, but our work (doi.org/10.1073/pnas.2213438120) has shown that these variations are quantifiable within the infraslow band (~0.01 Hz). Our next question is whether this REM infraslow periodicity is associated with neuropsychiatric domains, given the long-standing (but still inconsistent) links between REM sleep architecture, emotional regulation, and mood- or trauma-related symptoms. Using a cross-sectional polysomnographic dataset from male veterans enriched for these conditions, we examined n=59 for correlations between infraslow frequency of respiratory rate and 17 demographic and health variables, including age, neuropsychiatric scores, and sleep architecture metrics (excluding participants with moderate/severe sleep apnea). Our results indicated that REM respiratory rate - but not cardiac rate or EEG beta power - showed faster infraslow fluctuations in participants with a cluster of self-reported symptoms, including PTSD, anxiety, depression, pain, and poor cognitive function. No significant correlations were found between these symptoms and conventional REM metrics (e.g., REM latency, REM duration). We also analyzed the phase preference of rapid eye movements relative to infraslow fluctuations. As in our prior work, oculomotor activity was preferentially aligned with respiratory rate peaks, and this alignment did not change with symptom severity. This suggests that respiratory and oculomotor activity during REM co-accelerate as a function of the symptoms above, implying either faster or dysregulated REM temporal structure in these health conditions (e.g., disrupted alternation between tonic and phasic REM). These findings have implications for sleep-based neuropsychiatric biomarking and the timing of REM-dependent processes, such as memory consolidation.

Disclosures: L.S. Bueno-Junior: None. **P.T. Wickham:** None. **C.J. Tinsley:** None. **M.M. Lim:** None. **B.O. Watson:** None.

Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.02/GG12

Topic: G.07. Biological Rhythms and Sleep

Title: Sleep disruption in medical students across three countries: a multicenter behavioral analysis of institutional, gender, and bedtime determinants

Authors: *L. E. ÁLVAREZ-PALAZUELOS[1], **A. AHMAD**[2], C. DE LEON JUSINO[3], A. MORFFIZ GONZALEZ[4], F. AMEZQUITA NEGRON[2], S. HERNANDEZ[3], J. VELASCO[5], E. PAEZ MORALES[2], K. AHMAD[2], A. ARANDA[2];
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Abstract: Chronic sleep insufficiency disrupts hippocampal memory consolidation and prefrontal executive function, with particular impact on populations under sustained cognitive demand such as medical students. This multicenter preliminary study examined sleep patterns and behavioral disruptors across three universities in Mexico (Universidad Autónoma de Guadalajara, n=22), India (Shiv Nadar Institution of Eminence, n=203), and Egypt (Galala University, n=92), yielding a total sample of 317 undergraduate students. A standardized 33-item sleep habits questionnaire was administered independently at each site. Kruskal-Wallis and chi-square analyses were used to compare sleep behaviors across institutions, gender, and academic level. Sleep duration and mobile phone use were significantly associated with academic level and field of study ($p<0.01$), indicating that curricular demands modulate both sleep quantity and screen-based behavioral disruptors. Gender had limited influence on most sleep-related behaviors; significant differences were restricted to sleep latency, breathing discomfort, bad dreams, pain during sleep, and energy drink consumption, while bedtime, wake-up time, overall sleep quality, and mobile phone usage patterns did not differ significantly by gender. Bedtime emerged as a stronger and broader determinant of sleep quality, showing significant associations with sleep latency, nocturia, bad dreams, overall sleep quality, motivation, and phone-related sleep delay. Motivational impairment was reported by 59.1% of UAG participants, consistent with prefrontal dysfunction associated with chronic sleep restriction. These findings indicate that behavioral sleep timing is a more consistent modifiable factor than gender in driving sleep quality differences across diverse academic populations, and underscore the neurobiological relevance of bedtime-targeted interventions to mitigate sleep-driven cognitive burden in higher education.

Disclosures: L.E. Álvarez-Palazuelos: None. **A. ahmad:** None. **C. De Leon Jusino:** None. **A. Morffiz Gonzalez:** None. **F. Amezquita Negron:** None. **S. Hernandez:** None. **J. Velasco:** None. **E. Paez Morales:** None. **K. Ahmad:** None. **A. Aranda:** None.

Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.03/GG13

Topic: G.07. Biological Rhythms and Sleep

Support: CUHK (SBS & GCNI)
Hong Kong RGC (STG1/M-401/24-N)

Title: Day-night dynamics of brain states and behaviors revealed by 24-hour stereoelectroencephalography signals from epileptic patients

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Abstract: Many basic physiological processes in the brain and body are regulated by the brain's circadian rhythms. Yet, little is known about the neural underpinnings, dynamics, and functions of the day-night cycles of whole-brain activity in humans. Here, we exploited the stereoelectroencephalographic (SEEG) electrodes implanted in 4 epileptic patients (118-165 channels per subject) for monitoring seizures to probe activities of multiple cortical and deeper brain regions throughout the day. Continuous 24-hour SEEG and synchronized video data of the subjects were recorded for 2-7 days for brain state-behavior correlations. Throughout, subjects behaved normally without restrictions. Filtered SEEGs were re-referenced (bipolar method). Videos were manually annotated for different behaviors. Brain states were characterized by SEEGs' power spectral density (PSD) and functional networks based on correlations and coherence between channels. Unsupervised k-means clustering was used to identify common brain states over 24-hour periods. Similarities between timing of occurrence of brain states and behaviors were calculated using Jaccard coefficient. We first identified several recurrent frequency boundaries (~8, 13, 33, 65 Hz) which appeared as distinct discontinuities in PSD heatmaps and delineated frequency bands with distinct sleep-wake modulations. White-matter channels exhibited increased delta-band PSD and reduced high-frequency PSD during sleep. Brain states classified from interregional correlations showed state-dependent network organization, with eating-related states characterized by widespread inverse co-modulation and sleep-related states, by increased positive co-modulation. Coherence analysis revealed stable interhemispheric insular coupling in the delta band throughout the day, strong amygdala-hippocampal coupling in multiple bands during sleep and phone use, and two distinct beta-band sleep states involving language-related and hippocampal-limbic networks. Our findings show that coordinated day-night cycles of activity can be identified in multiple brain regions, but their temporal co-fluctuation and spectral coupling are flexibly modified to accommodate specific behaviors.

Disclosures: T. Yu: None. **C. Yao:** None. **C. Han:** None. **H.R. Chan:** None. **V. Cheung:** None.

Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.04/GG14

Topic: G.07. Biological Rhythms and Sleep

Support: the National Major Science and Technology Project for Brain Science and Brain-like Intelligence Technology–National Science and Technology Major Project (2025ZD0218200)
the National Natural Science Foundation of China General Program (82271527), and the Beijing Nova Program (20230484320)

Title: Sleep disturbance is associated with age-dependent and nonuniform connectome aging

Authors: S. QU[1], C. CHEN[1], M. ZHANG[2], X. LIU[1], Z. WANG[1], C. ZHANG[2], X. LIN[1], S. WANG[1], J. DENG[1], J. SHI[3], L. LU[1], ***L. SHI**[1];
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Abstract: Background: Sleep disturbance (SD) is associated with cognitive decline, yet its relationship with connectome aging remains unclear. This study therefore focused on four objectives: the association between SD and connectome age, variation in this association across adulthood, the distribution of brain ageing across functional networks, and the SD-associated networks most closely related to cognition. **Methods:** Using multimodal connectome data from the UK Biobank, we analyzed 8,264 healthy controls and 240 patients with SD. Brain age was estimated from structural connectivity (SC), functional connectivity (FC), and structure-function coupling (SFC), using both full connectivity matrices and macroscale gradients. We quantified whole-brain and network-level brain-age gaps (BAGs), modeled their age-related trajectories, evaluated variation across functional networks, and examined associations between network-specific BAGs and fluid intelligence. **Results:** Patients with SD showed an older-appearing connectome across SC, FC, and SFC, and the findings remained consistent across alternative SD definitions. Group differences were limited in midlife and became more evident with advancing age, reaching approximately 2-3 years in older adults. At the network level, larger differences were observed in higher-order association systems, including the default-mode and frontoparietal-control networks. By contrast, sensorimotor and salience/ventral-attention networks showed smaller differences. Higher BAGs in association systems were related to poorer fluid intelligence, with the clearest association observed in the default-mode network. **Conclusion:** SD is associated with an older-appearing connectome, with differences that vary across age and functional networks, with more evident in later life and are concentrated in higher-order association systems. The association with poorer fluid cognition is particularly apparent in the default-mode network. These findings suggest that connectome aging in SD may

involve selective vulnerability of age-dependent and higher-order systems rather than a uniform shift across the age and brain.

Disclosures: S. Qu: None. **C. Chen:** None. **M. Zhang:** None. **X. Liu:** None. **Z. Wang:** None. **C. Zhang:** None. **X. Lin:** None. **S. Wang:** None. **J. Deng:** None. **J. Shi:** None. **L. Lu:** None. **L. Shi:** None.

Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.05/GG15

Topic: G.07. Biological Rhythms and Sleep

Title: Enhancing Sleep Assessment in Deployed Veterans: Linking Subjective Sleep Quality to Actigraphy

Authors: *M. BAIME[1,2,3], N. ALLEN[2], K. PIETRO[2,3], L. RECK[1,2,3], C. LU[1,2,3], K. POLLIN[2], M. COSTANZO[2,3,4], C. BRENEMAN[1,2,3], M. REINHARD[2,3,5];
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Abstract: Sleep disturbances are highly prevalent among Veterans, making accurate assessment of sleep quality critical for improving health outcomes and reducing symptom burden. Comprehensive evaluation should include both subjective and objective assessments to capture the multidimensional nature of sleep in order to accurately assess medical readiness. However, relying on averaged sleep scores assumes stable sleep patterns and may obscure nightly variation. The current analysis examines the link between subjective sleep quality and actigraphy across multiple nights, emphasizing within-person variability in deployed Veterans. Baseline data from a longitudinal study investigating military exposures were used in these analyses (n=50, age=49.1±8.4y, 88% male). Sleep was measured using wrist-worn actigraphy devices and sleep diaries over multiple nights. Sleep quality was rated each morning using a five-point scale ranging from “very poor” to “very good”. Actigraphy data were manually scored to derive sleep efficiency (SE), total sleep time (TST), wake after sleep onset (WASO), motor activity counts (MAC), and number of awakenings (NWAK). Post-Traumatic Stress Disorder (PTSD) and depression symptoms were assessed via the PTSD Checklist for *DSM-5* (PCL-5) and Patient Health Questionnaire-9 (PHQ-9). Linear mixed effects models were fit to examine the relationship between subjective sleep quality and actigraphy. Veterans had elevated PTSD (PCL-5: 31.5±22.6) and depression (PHQ-9: 11.2±6.5) scores. Higher within-subject sleep quality ratings were associated with greater TST and SE and less MAC and WASO ($p < .05$). These associations were statistically significant after adjusting for day index, age, PCL-5 and PHQ-9. No between-subject differences in average sleep quality rating and actigraphy were found.

Veterans' within-subject sleep quality ratings were associated with actigraphy parameters (TST, SE, MAC, WASO). On nights when a participant rated sleep quality better than their average, they showed objectively less movement and wakefulness with more total sleep time and higher efficiency, indicating that nightly ratings capture unique variance beyond symptom severity. This multi-night framework reduces trait-level bias and supports a comprehensive view of sleep health. Granular sleep assessments that more accurately detect within-person sleep disturbances in Veterans may be essential for improving sleep quality and overall wellbeing.

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Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.06/GG16

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01HL171813
NIH K25HL151912
NIH R21HL165320

Title: Time-on-task effects in sleep apnea patients on and off treatment

Authors: *V. BUILOFF, D. Z. AZAD, D. I. VALENCIA, S. WICKRAMARATNE, K. KAM, L. FLEYSHER, A. W. VARGA, I. AYAPPA, D. M. RAPOPORT, A. PAREKH;
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Abstract: Obstructive sleep apnea (OSA) is associated with sleepiness and impaired vigilance. The psychomotor vigilance task (PVT) is a well-established, noninvasive measure of vigilance in OSA. Time-on-task (ToT) effects during the PVT can reveal fatigue-related declines in performance. However, OSA effects on ToT are not fully understood. We compared global and thalamic neural activity between the first and last 2 minutes of the PVT in patients on and off continuous positive airway pressure (CPAP) therapy to assess differences in sustained attention. Thirty-one participants (58.1% male; age 56.5±11.6 years) were included. Participants performed a 20-minute PVT during fMRI after in-lab polysomnography. Twenty-two participants completed paired on/off CPAP sessions (44 total), contributing up to two PVT runs per session for a total of 79 runs analyzed. Analyses were performed in AFNI. The estimated magnitude of neural response, indicated by a mean beta coefficient, served as the primary measure. Mean beta differences were calculated as first 2 − last 2 minutes of PVT. Clusters ≥20 voxels (global) or ≥10 voxels (thalamus) at $p \leq 0.05$ were considered significant. Response speed (1/reaction time) served as the secondary measure. Both CPAP conditions demonstrated greater neural activity during the last versus first 2 minutes of the PVT in global and thalamic analyses (Fig 1A-B, $p<0.05$). Negative beta values reflected increased late-task activation, which was greater on

CPAP, particularly in the thalamus. Response speed showed less decline on CPAP than off CPAP ($p = 0.05$). The increase in neural activation from early to late PVT suggests greater recruitment of neural resources to sustain attention with prolonged task engagement. These findings align with prior work showing compensatory increases in arousal and thalamocortical engagement under rising cognitive demand (Roose et al. 2026). Participants on CPAP demonstrated a greater increase in late-task activation than those off CPAP, potentially indicating more effective compensatory recruitment during sustained attention.

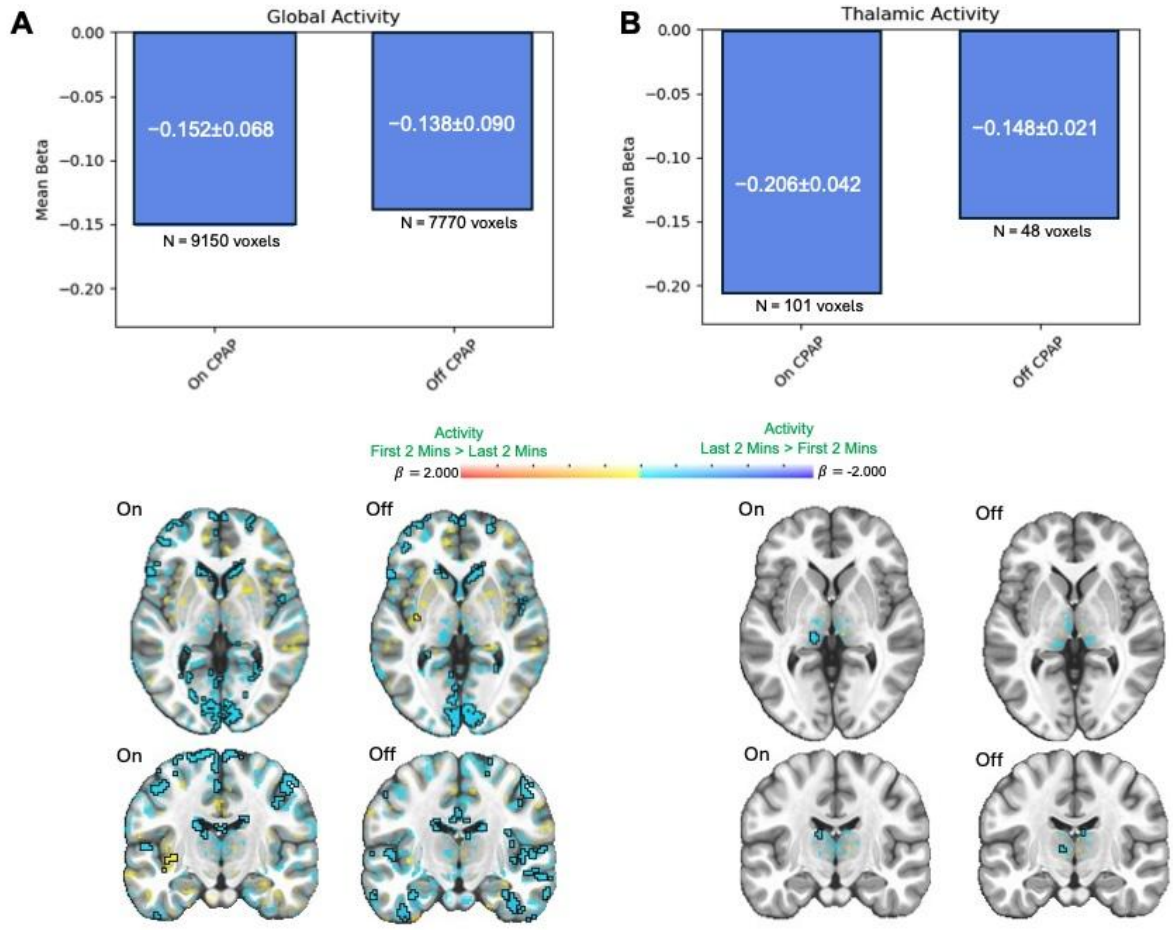


Fig. 1 Global (A) and thalamic (B) mean change in neural activity between the first and last two minutes of the PVT by condition. Mean beta differences were calculated as first 2 minutes − last 2 minutes. Color bar values represent beta coefficients in the activation maps: more blue = greater activity during the last two minutes, more red = greater activity during the first two minutes. Voxel counts (N) represent clusters surviving a minimum size threshold of 20 voxels (whole brain) or 10 voxels (thalamus) at $p \leq 0.05$. CPAP - continuous positive airway pressure.

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Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.07/Web Only

Topic: G.07. Biological Rhythms and Sleep

Support: DOD - Congressionally Directed Medical Research Programs (CDMRP) NFRP

Title: Longitudinal, objective measurement and analysis of sleep-wake patterns in NF-1 patients

Authors: *A. PETTI[1], J. A. WALKER[1,2], J. M. BRAIT[1], I. BURTCH[1], N. KANGETI[1], S. MUNN[1], S. J. BOULEY[1,2], H. S. DASHTI[1,3], J. L. NOSKER[1,2], E. B. KLERMAN[1,2], M. W. PARSONS[1,2], R. SAXENA[1,3];
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Abstract: Purpose: Sleep disturbances and poor sleep quality are frequently reported but underexplored in people with neurofibromatosis type 1 (NF1). Inadequate sleep can have adverse effects on daytime functioning by impacting metabolism, mood regulation, cognition, and immune function. Our study aimed to characterize sleep and circadian phenotypes associated with NF1 and test their dynamic relationship with pain and cognitive function. Methods: We performed a clinical research study of sleep, circadian rhythms, cognition, and quality of life in 100 adult patients with a clinical or molecular diagnosis of NF1 and 100 controls matched for age, sex, race, and ethnicity. Objective metrics of sleep quantity, quality, timing, and regularity as well as circadian rest-activity rhythms were obtained through wrist actigraphy, and participants completed subjective online questionnaires on sleep and daily sleep logs over a 2-week period. Participants also completed a series of cognitive assessments through the TestMyBrain website every morning, including tests on Verbal Paired Associates Memory, Digital Symbol Matching, Trail Making, and Continuous Performance. We tested associations between summary sleep metrics and NF1 status using linear or logistic regression adjusted for matching factors. Results: The study population was ~85% white, had a mean age of ~41 years and was 75% female. NF1 patients reported shorter time in bed (-34.8 (10.2) min per night; $p<.001$) and longer time to fall asleep (~31.4 (9.1) min; $p<.001$) than controls based on daily sleep logs. Insomnia Severity Index (ISI) scores indicated more severe insomnia symptoms in NF1 patients ($p<.001$) and poorer sleep quality as measured by Pittsburgh Sleep Quality Index ($p<.000001$). Epworth Sleepiness Scale (ESS) scores were comparable across groups, suggesting similar daytime sleepiness levels. However, patients reported poorer functional outcomes related to sleep (FOSQ; $p<.001$). Preliminary analyses of 14-day actigraphy data suggest milder disruptions in objective sleep metrics than those observed in self-reported measures. Conclusion: Our study confirmed significant self-reported sleep disturbances, particularly with sleep duration and quality, in patients with NF1 as compared to an age-, race-, and sex-matched control population. Interventions that improve sleep in the general population may be beneficial in this population. The observed sleep disturbances highlight the need to better understand their associations with pain and cognitive function in NF1.

Disclosures: A. Petti: None. **J.M. Brait:** None. **R. Saxena:** None.

Poster

PSTR369: Sleep: Human Behavioral Studies

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Program #/Poster #: PSTR369.08/GG17

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant R61 HL154095
NIH Grant R33 HL154095

Title: Identifying Sleep Architecture Phenotypes in Premature NICU Infants

Authors: *K. GRAHAM[1], J. D. BARKS[2], S. V. GLISKE[3];
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Abstract: Sleep is thought to play a critical role in early neurodevelopment, supporting processes from neural connectivity to synaptic development. However, premature infants in the Neonatal Intensive Care Unit (NICU) experience significant sleep disruptions. Research suggests environmental factors and medical interventions frequently needed in the NICU can delay hospital discharge and create adverse effects for the developing brain. Despite this, the structure and quality of sleep in this atypical environment remain poorly understood. This gap represents a critical need for research, as the first step is determining whether distinct sleep patterns exist in this population. Our objective was to identify and characterize sleep bout architecture in premature NICU infants using data-driven methods. Retrospective analysis was conducted from polysomnogram recordings of premature infants recorded at the University of Michigan Motts Children's Hospital. With IRB approval and informed consent from patients' guardians, recordings were collected from thirty-seven premature infants. Patients ranged in age from 30 to 38 weeks gestational age. Sleep bouts, defined as continuous periods of one specific sleep state, were identified and quantified from EEG recordings, resulting in distinct features for each infant. Dimensionality reduction of features was performed using principal component analysis (PCA) with varimax rotation, which identified 13 components explaining 95% of total variance. K-means clustering was then applied to identify patterns between patients and sleep architecture. Two distinct clusters were identified across infants. Validation of these clusters via a permutation test of 10,000 iterations further confirmed that a two-cluster separation was not due to random chance but rather a clear distinction between two groups of patients. Centroid variance accounted for 8-11% of total variance, further indicating consistent and meaningful separation between clusters. These findings suggest that sleep in premature NICU infants is not uniform. The identification of two distinct groups of patients suggests that not all premature infants experience sleep in the NICU in the same way. Characterizing these patterns is a critical first step toward understanding the neurodevelopmental implications of disrupted sleep in this population.

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Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.09/GG18

Topic: G.07. Biological Rhythms and Sleep

Title: Wireless EEG/EMG Telemetry for Preclinical Sleep Pharmacology Assessment

Authors: *X. XU;
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Abstract: Preclinical sleep-wake evaluation remains a key challenge for CNS drug development, particularly for novel hypnotics such as dual orexin receptor antagonists (DORAs). We implemented a high-throughput wireless telemetry EEG/EMG platform from Data Sciences International (DSI), which enables simultaneous, long-term recording from up to 32 freely moving rodents. A key advantage of this wireless system over traditional tethered setups is the elimination of movement restrictions and stress-related artifacts, thereby allowing natural sleep-wake behavior and more reliable data collection over extended periods. The system captures cortical EEG activity, EMG activity, and locomotor activity, from which we derive wake, NREM, and REM durations, as well as sleep latency, sleep bout number, and fragmentation indices. In this study, we evaluated the platform performance using reference DORAs. In studies using male SD rats or C57BL/6J mice under 24-hour continuous recordings, the platform demonstrated that DORA treatment reduced wakefulness, significantly shortened the latency to persistent NREM sleep, and increased total NREM duration without altering EEG power spectra. These effects are consistent with the induction of physiological sleep rather than pathological sedation. Assay specificity and sensitivity were confirmed using pharmacological controls, including caffeine for wake promotion, diazepam for hypnotic effects, and olanzapine for sedative effects. Beyond DORAs, we evaluated the translational relevance of the platform using the 5xFAD mouse model of Alzheimer's disease. We characterized sleep architecture and EEG power spectra in 5xFAD versus wild-type mice. The 5xFAD mice recapitulated key human sleep disturbances: increased wake fragmentation, reduced NREM/REM sleep, daytime napping, and prolonged sleep latency. They also exhibited significant EEG power spectral alterations. Notably, delta power decreased during both NREM and REM sleep, whereas theta power increased during REM sleep. These spectral changes reflect disrupted sleep homeostasis and cortical network dysfunction, offering a quantitative electrophysiological signature of AD-related pathology. Importantly, EEG power spectrum endpoints enable sensitive detection of disease progression and serve as translational biomarkers for evaluating interventions aimed at restoring normal sleep architecture and cortical dynamics. In summary, this wireless EEG/EMG platform

enables high-throughput, physiologically relevant characterization of sleep-wake dynamics and provides a robust translational framework for preclinical sleep pharmacology.

Disclosures: X. Xu: None.

Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.10/GG19

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01 HL 169995

Title: Early Sleep EGG and Cognitive Ability Predict Later Nap Transitions During Infancy

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Abstract: Infancy is a period of rapid brain maturation, and sleep is believed to play a central role. Slow wave activity (i.e., delta activity; SWA) is a marker for cortical maturation and is associated with greater long-term potentiation (LTP), the cellular mechanism underlying memory storage and brain development. The transition from triphasic to biphasic sleep (3 to 2 sleep bouts/day) is posited to reflect neural maturation. The current research examines longitudinal relations between sleep EEG features (i.e., SWA) and measures of cognitive ability on timing of sleep transitions. Reduced naps in infancy are speculated to reflect greater developmental maturation of the brain; as such, we hypothesized that topography of SWA and cognitive scores at 9 months would both predict sleep transitions at 12 months. Infants (n=27) underwent polysomnography (PSG) during a morning nap, and completed a cognitive assessment (Bayley Scales of Infant Development). By 12 months, nap habituality was assessed using actigraphy data and caregiver-filled sleep diaries to classify triphasic (n=15) and biphasic (n =12) sleepers. EEG-derived frontal/occipital (F/O) ratios of SWA and cognitive measures obtained at 9 months were examined as predictors of nap habituality at 12 months. At 9 months, infants who transitioned to biphasic sleep by 12 months exhibited higher Bayley-IV Cognitive Standard Scores ($z = 3.31$, $p = 0.001$) and F/O ratios ($z= 2.0$, $p = 0.048$) than infants who remained triphasic, both showing a significant difference between nap groups. Linear regression showed that the F/O ratio accounted for 15.9% of the variance in nap groups ($R^2 = 0.159$, $p = 0.039$), and cognitive scores accounted for 30.3% ($R^2 = 0.303$, $p = 0.003$). These findings suggest both SWA topography and cognitive performance are associated with nap cessation during infancy. Higher F/O ratios (more mature, frontal SWA) and cognitive scores at 9 months were associated with biphasic sleep by 12 months. SWA may promote neural plasticity, which may

underlie the behavioral and subsequent changes in sleep. Taken together, the results support the idea that nap transitions may reflect developmental maturation in infancy.

Disclosures: A.E. Katasema: None. **M.N. Horger:** None. **J.F. Holmes:** None. **N. Flores:** None. **R.M. Spencer:** None.

Poster

PSTR369: Sleep: Human Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.11/GG20

Topic: G.07. Biological Rhythms and Sleep

Support: SECIHTI Grant CBF-2025-G-698

Title: Multilevel Risk Profiles of Problematic Gaming and Sleep Disturbances in Mexican Children and Adolescents: An Unsupervised Machine Learning Study

Authors: *V. HUERTA[1], S. TREJO GARCIA[2], S. QUIÑONES BELTRAN[3], J. RAMOS-LOYO[4], L. LLAMAS-ALONSO[3];
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Abstract: Problematic gaming and sleep disturbances are growing public health concerns among children and adolescents, yet evidence from Latin American populations, particularly Mexico, remains limited. This study characterized multilevel risk profiles associated with both conditions in Mexican youth using unsupervised machine learning. A population-based, cross-sectional sample of 1,221 participants (M = 10.45 years, SD = 2.34; 49.5% female) from public and private schools across multiple regions of Mexico was evaluated via parent- and child-reported measures assessing gaming habits, Internet Gaming Disorder (IGD) symptoms, sleep disturbances, neurodevelopmental conditions, family context, and socioeconomic variables. Spearman correlation analyses showed significant associations between gaming exposure, problematic symptoms, and multiple sleep disturbance indicators. Weekly gaming hours correlated positively with IGD symptoms and daytime somnolence, and measures converged strongly across parent and child reports. To identify latent behavioral phenotypes, Hierarchical Density-Based Spatial Clustering of Applications with Noise (HDBSCAN) was implemented following a multistage preprocessing pipeline integrating clinical, behavioral, and contextual variables. The clustering solution revealed heterogeneous risk profiles ranging from low-risk groups to clinically elevated phenotypes. Notably, the outlier/noise cluster consistently exhibited the highest problematic gaming scores and most severe sleep symptomatology across both parent- and child-reported measures, suggesting atypical high-risk behavioral profiles. Intermediate clusters displayed subclinical elevations, supporting dimensional conceptualizations of problematic gaming rather than categorical distinctions. These findings highlight the utility of

unsupervised machine learning approaches for identifying clinically meaningful behavioral phenotypes and understanding these disturbances within the sociocultural context of Mexican youth.

Disclosures: V. Huerta: None. **S. Trejo Garcia:** None. **S. Quiñones Beltran:** None. **J. Ramos-Loyo:** None. **L. Llamas-Alonso:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.01/GG21

Topic: G.08. Food and Water Intake and Energy Balance

Support: NRF Grant NRF-2022M3A9F3094559
NRF Grant RS-2023-00208193
NRF Grant RS-2024-00404471
NRF Grant RS-2024-00403511
NRF and Ministry of Education Grant BK21 FOUR

Title: Neural Circuits for Dehydration-Induced Anorexia and Its Reversal

Authors: *H. KIM, Y. JEONG;
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Abstract: Feeding and drinking are fundamental behaviors essential for maintaining body homeostasis. Although extensive research has independently examined the neural circuits regulating each process, the interaction between feeding and drinking mechanisms remains poorly understood. To investigate this interaction, we employed a dehydration-induced anorexia (DIA) model using repeated dehydration-rehydration cycles. Following chronic dehydration, water access rapidly restored feeding behavior, a phenomenon we termed rehydration-induced feeding (RIF). We next monitored arcuate AgRP neuron activity using fiber photometry to examine the neural basis of this behavioral response. Rehydration robustly activated AgRP neurons, and this response became progressively stronger with increasing dehydration severity. Notably, both RIF and AgRP activation were selectively induced by hypotonic rehydration. This finding suggests that AgRP activation is not driven simply by fluid ingestion or gastric distension, but rather by signals associated with restoration of hydration state. Consistent with these observations, chemogenetic activation of AgRP neurons was sufficient to overcome dehydration-induced anorexia, whereas inhibition markedly attenuated rehydration-induced feeding, demonstrating a critical role for AgRP neurons in both DIA and RIF. Because rehydration rapidly suppresses activity within canonical thirst circuits, we hypothesized that inhibition of SFO/MnPO Nos1 neurons might be sufficient to trigger feeding recovery. However, Nos1 inhibition failed to restore feeding behavior, suggesting that additional neural substrates mediate feeding recovery following rehydration. To identify candidate circuits involved in this

response, we performed whole-brain cFos mapping following chronic rehydration. This analysis revealed activation across multiple brain regions, including several hindbrain nuclei. Further cell-type characterization revealed substantial recruitment of GABAergic neurons, highlighting inhibitory populations as potential mediators of feeding recovery. Together, these findings identify rehydration-induced feeding as a distinct behavioral transition characterized by AgRP activation and recruitment of hindbrain neuronal populations. Our results suggest that thirst quenching re-engages feeding circuits following chronic dehydration, revealing a potential mechanism linking fluid homeostasis to feeding behavior.

Disclosures: H. Kim: None. **Y. Jeong:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.02/GG22

Topic: G.08. Food and Water Intake and Energy Balance

Support: FAPESP
CNPq

Title: NaCl intake in rats treated with moxonidine into the lateral parabrachial nucleus combined with isoproterenol intraperitoneally

Authors: *P. M. DE PAULA[1], P. A. A. GOIS[2], C. A. ANDRADE[3], D. S. COLOMBARI[4], E. COLOMBARI[5], L. A. DE LUCA, Jr.[6], J. MENANI[2];
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Abstract: The lateral parabrachial nucleus (LPBN) is a structure located in the pons that integrates important role in inhibitory mechanisms that control water and, especially, NaCl intake. The injection of moxonidine (alpha2-adrenergic/imidazoline receptor agonist) into the LPBN increases NaCl intake induced by central injection of angiotensin II. Isoproterenol (β-adrenergic receptor agonist) causes hypotension, renin release, and water intake upon peripheral administration, but does not stimulate sodium intake. In the present study we investigated the effects of bilateral injections of moxonidine (0.5 nmol/200 nl) into the LPBN on water and 0.3 M NaCl intake after intraperitoneal (ip) injection of isoproterenol (30 ug/kg of body weight). Male Holtzman rats (300-350 g, n=6) with stainless steel cannulas implanted bilaterally into the LPBN were used. The experimental protocols were approved by the Ethical Committee for Animal Care and Use - CEUA of the Dentistry School of Araraquara, UNESP (Proc. CEUA nº 17/2025). The combination of ip isoproterenol with bilateral injections of moxonidine into the LBPN induced significant ingestion of 0.3 M NaCl (17±6.6, vs. vehicle/propyleneglycol: 1.3±0.7 ml/120 min,

p<0.05), but did not change water intake (6.0±2.0, vs. vehicle/propyleneglycol: 2.7±0.9 ml/120 min). The results suggest that the treatment of the LPBN with moxonidine reduces the activation of the inhibitory mechanisms facilitating NaCl intake after ip injection of isoproterenol.

Disclosures: P.M. De Paula: None. **P.A.A. Gois:** None. **C.A. Andrade:** None. **D.S. Colombari:** None. **E. Colombari:** None. **L.A. De Luca:** None. **J. Menani:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.03/GG23

Topic: G.08. Food and Water Intake and Energy Balance

Support: R01HL152166

Title: Renal interoceptive signaling drives sodium appetite following acute sodium depletion

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[1]Dept. of Integrative Biol. & Physiol., [2]Dept. of Psychology, [3]Div. of Nephrology and Hypertension, [4]Div. of Autonomic Neuromodulation, Univ. of Minnesota, Minneapolis, MN; [5]Dept. of Physiol., Univ. Federal de São Paulo, São Paulo, Brazil

Abstract: Sodium appetite is essential for restoring extracellular fluid balance following sodium loss. However, the sensory pathways that convey information about sodium status to the brain and activate the neural circuits driving this behavior remain poorly understood. We previously identified an interoceptive role for the kidneys in regulating salt intake in a rat model of primary aldosteronism. We found that selective ablation of the afferent renal nerves (ARDN; kidney-to-brain) reduced saline intake without affecting water intake. Here, we tested whether afferent renal nerves contribute to compensatory saline intake following acute sodium and volume depletion.
Male Long-Evans rats (7-8 weeks old; sham-replete n=3, sham-deplete n=4, afferent renal denervation (ARDN-deplete n=4) were single-housed with free access to water and standard chow prior to the experiment. ARDN was performed by periaxonal application of capsaicin (33 mM) to the renal arteries. Sham rats had their renal arteries isolated but not treated. Baseline water and saline intake were measured over 5-days before the depletion challenge. To induce acute sodium depletion, rats received subcutaneous injections of furosemide (10 mg/kg s.c.) and captopril (5 mg/kg s.c.) or received a saline injection. After 60 minutes, rats were given free access to two bottles: one containing deionized water (dH_2O) and the other hypertonic saline (1.8% NaCl) for 2 hours. Statistical analyses were performed using a linear mixed-effects model with Tukey's post hoc comparisons.
ARDN-deplete rats consumed less saline than both sham-deplete and sham-replete rats (1.6 vs. 7.4 vs. 8.2 mL/24hr/100g BW, respectively; $P < 0.001$) at baseline, indicating that renal afferent

nerves contribute to voluntary sodium intake under basal conditions. Following sodium depletion, cumulative 2-hour saline intake was significantly greater in sham-deplete rats than in ARDN-deplete and sham-replete rats (19.4 vs. 6.8 vs. 9.6 mL/100g BW, respectively; $P < 0.0001$). Saline intake did not differ between ARDN-deplete and sham-replete rats ($P > 0.05$). Water intake was similar among all groups (all $P > 0.05$).
These findings demonstrate that kidney-to-brain signaling contributes to the behavioral response to acute sodium depletion, as selective lesioning of kidney afferent nerves was sufficient to reduce saline intake without affecting water intake. Ongoing studies are using lickometry to characterize temporal patterns of salt intake and fiber photometry to examine dopamine signaling in the nucleus accumbens, with the aim of determining whether afferent renal nerves influence the motivational and rewarding component of sodium appetite.

Disclosures: B. Anidu: None. **A. Costa Veiga:** None. **L. Ye:** None. **A. Dayton:** None. **K.M. Fraser:** None. **L. Evans:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.04/GG24

Topic: G.08. Food and Water Intake and Energy Balance

Title: Ventricular Expansion Couples Hyperosmotic Stress to Thirst

Authors: *Z. QIU;
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Abstract: Thirst is thought to arise from osmotic signals detected by circumventricular organs, yet how hyperosmotic stress activates mechanosensitive channels remains unclear because cell shrinkage should reduce membrane tension. Here we identify a brain-scale mechanical signal that couples systemic osmotic stress to drinking. In mice, hypertonic saline rapidly increased serum and cerebrospinal fluid osmolality, expanded the lateral ventricles, and enhanced SFO activity and water intake. Relieving or blocking ventricular deformation attenuated SFO responses and drinking without eliminating osmotic gradients. Hyperosmotic challenge also produced localized deformation of periventricular cells, where spatial transcriptomics revealed candidate mechanosensitive channels, including Tmem63b and Piezo1. Thus, ventricular expansion provides a mechanical component of osmotic thirst, uncovering an osmo-mechanical layer of interoceptive regulation.

Disclosures: Z. Qiu: None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.05/HH1

Topic: G.08. Food and Water Intake and Energy Balance

Support: FAPESP
CNPq

Title: Interaction between the medial septal area and the lateral parabrachial nucleus in the control of sodium intake

Authors: *J. MENANI, P. M. DE PAULA, C. A. ANDRADE, E. COLOMBARI, D. S. COLOMBARI, L. DE LUCA;
UNESP, Araraquara, Brazil

Abstract: The deactivation of the inhibitory mechanisms for sodium appetite with moxonidine (α_2 adrenergic/imidazoline agonist) injected into the lateral parabrachial nucleus (LPBN) strongly increases the natriorexigenic response to angiotensin II (ANG II) injected intracerebroventricularly. It has also been shown that ANG II injected into the medial septal area (MSA) stimulates water, not NaCl intake. In the present study, we tested if angiotensinergic AT1 receptor activation in the MSA combined with moxonidine into the LPBN would induce NaCl intake. Male Holtzman rats with stainless steel cannulas implanted into the MSA and bilaterally into the LPBN were used. ANG II (10 ng/0.5 µl) injected into the MSA combined with moxonidine (0.5 nmol/0.2 µl) into the LPBN produced marked ingestion of 0.3 M NaCl (15.9±4.7 ml/120 min) compared to only ANG II into the MSA (1.1±0.4 ml/120 min). The injection of moxonidine into the LPBN also strongly increased 0.3 M NaCl intake in rats treated with the diuretic furosemide + captopril (angiotensin converting enzyme inhibitor) subcutaneously (30.9±4.7, vs. vehicle: 3.0±1 ml/120 min). The pre-treatment with losartan (ANG II AT1 receptor antagonist, 1 or 10 µg/0.5 µl) into the MSA reduced 0.3 M NaCl intake in rats treated with ANG II + moxonidine (4.0±2.4 ml/120 min) or rats treated with furosemide + captopril + moxonidine (13.4±4.8 ml/120 min). Similar results were produced on water intake. The results suggest that AT1 receptor activation in the MSA facilitates NaCl intake, an effect strongly inhibited by the LPBN inhibitory mechanisms.

Disclosures: J. Menani: None. **P.M. De Paula:** None. **C.A. Andrade:** None. **E. Colombari:** None. **D.S. Colombari:** None. **L. De Luca:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.06/HH2

Topic: G.08. Food and Water Intake and Energy Balance

Support: DK133818 (DD)

Title: Glucagon-like peptide-1 control of water intake through the anteroventral third ventricle region

Authors: *S. A. DAVID[1], M. N. PEARSON[2], J. SIRKIN[2], D. J. BRAKEY[2], M. J. PAUL[1], D. DANIELS[3];
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Abstract: The mechanisms controlling fluid and food intakes are intertwined, making it challenging to separate the specific neural and hormonal pathways that control each behavior. For instance, glucagon-like peptide-1 (GLP-1) has a role in the suppression of both food and fluid intakes, without clarity about sites of overlap and nonoverlap. The vasopressin-deficient Brattleboro rat provides a unique model to study the thirst-specific elements of the GLP-1 system. Brattleboro rats are polydipsic, and hyper-responsive to the fluid intake suppression caused by GLP-1 receptor (GLP-1R) agonist treatment, but show a hypophagic response to the treatment that is indistinguishable from that observed in wildtype rats. To better understand the brain regions that differ between Brattleboro rats and their wildtype littermates, we examined Fos- and GLP-1R-immunoreactivity after dehydration with or without subsequent access to water. These analyses revealed several areas with main effects of water access or genotype, but the anteroventral third ventricle (AV3V) region had an interaction effect in both the number of Fos-positive cells and the density of GLP-1R-immunoreactivity. We therefore hypothesized that GLP-1 selectively regulates drinking through specific neural circuits converging on the AV3V, rather than through broad activation of eating-related pathways. In support of this hypothesis, we found that direct administration of the GLP-1R agonist Exendin-4 into the AV3V robustly reduced drinking without affecting eating and observed a selective suppression of drinking when we chemogenetically excited AV3V-projecting neurons in the caudal brainstem. To identify caudal brainstem neurons recruited after drinking, an activity-dependent Targeted Recombination in Active Populations (TRAP) virus was injected into the caudal brainstem and a Cre-dependent retrograde Designer Receptor Exclusively Activated by Designer Drugs (DREADD) virus was injected into the AV3V. AV3V-projecting cells then were TRAPed during drinking and subsequently stimulated chemogenetically to test for effects on eating or drinking. We observed suppression of drinking, but not eating, when these neurons were chemogenetically excited. These findings are consistent with the model that GLP-1-related signals from the hindbrain converge on the AV3V to suppress thirst.

Disclosures: S.A. David: None. **M.N. Pearson:** None. **J. Sirkin:** None. **D.J. Brakey:** None. **M.J. Paul:** None. **D. Daniels:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.07/HH3

Topic: G.08. Food and Water Intake and Energy Balance

Support: R01DK122811

Title: GLP-1 receptor activation in the dorsal hindbrain lowers blood glucose and alters excitability of vagal motor neurons in hyperglycemic mice

Authors: K. C. SMITH, L. CANTU, M. C. MOSELEY, *B. N. SMITH;
Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: The gastric protein hormone glucagon like peptide 1 (GLP-1) lowers blood glucose when administered peripherally, and longer lasting GLP-1 receptor (GLP1R) agonists have been employed to improve blood glucose regulation in type 2 diabetes. Proposed mechanisms underlying the effects of GLP1R agonism do not fully explain the observed effects on blood glucose. Central GLP1R in the dorsal vagal complex may contribute, but studies to identify how GLP1R activation in hindbrain neurons contributes to autonomic control of systemic glucose regulation have not been done. Within the dorsal hindbrain, second order viscerosensory neurons of the nucleus tractus solitarius, chemosensory neurons of the area postrema, and parasympathetic motor neurons of the dorsal motor nucleus of the vagus (DMV) express GLP1R receptors and their activity regulates visceral homeostatic processes, including energy balance. This study tested the hypothesis that GLP1R activation in the hindbrain alters DMV neuron excitability and lowers blood glucose concentration in chronically hyperglycemic mice. Fourth ventricle administration of the GLP1R agonist, exendin-4 (Ex-4; 0.1 μg) produced negligible effects on blood glucose concentration in control mice, but induced a significant ($p<0.05$), peripheral muscarinic receptor-dependent decrease in systemic hyperglycemia for >4 hours in streptozotocin (STZ)-treated, hyperglycemic mice, a model of type 1 diabetes. Patch-clamp recordings from DMV neurons in vitro revealed that Ex-4 (100nM) application altered synaptic properties of DMV neurons, with the balance of Ex-4 effects being significantly enhanced by a recent history of systemic hyperglycemia. These findings identify central parasympathetic circuitry as a novel target for glucose regulating effects of GLP1R activation and suggest that GLP1R agonists acting in the dorsal hindbrain can alter vagal output to produce its beneficial metabolic effects.

Disclosures: K.C. Smith: None. **L. Cantu:** None. **M.C. Moseley:** None. **B.N. Smith:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.08/HH4

Topic: G.08. Food and Water Intake and Energy Balance

Title: CNS-penetrant NLRP3 inhibitor achieves durable weight loss and reverses hypothalamic inflammation in diet-induced obesity

Authors: J. L. GUO, ***T. P. BACHOR**, D. BRAUN, B. HUFFMAN, G. FITZGERALD, M. LIU, M. AGAM, X. WANG, E. SUN, B. FOX, M. STEFFEK, T. FISCHER, R. A. CRAIG II, E. YULYANINGSIH;
Tenvie Therapeut., Brisbane, CA

Abstract: The NLRP3 inflammasome is a key mediator of innate immunity that integrates inflammatory and metabolic stress signals. Increased and/or chronic activation of this critical pathway has been implicated in obesity, with hypothalamic neuroinflammation linked to dysregulation of energy balance. TN-783 is an investigational, CNS-penetrant, small-molecule NLRP3 inhibitor that potently suppressed inflammasome activation across multiple in vitro assays. In diet-induced obese (DIO) mice, only TN-783, and not the peripherally restricted NLRP3 inhibitor TN-101, produced progressive and sustained weight loss, underscoring the requirement for central target engagement. Weight loss was driven by a persistent reduction in food intake across both acute and chronic phases, without altering energy expenditure. This effect was further characterized by selective reduction of fat mass, with minimal impact on lean tissues. Mechanistically, NLRP3 inhibition attenuated DIO-induced hypothalamic neuroinflammation and partially reversed obesity-associated molecular changes based on transcriptomic and proteomic profiling of the hypothalamus. Beyond monotherapy, TN-783 enhanced the effects of the GLP-1 receptor agonist semaglutide by amplifying weight loss, reinitiating weight loss after semaglutide effect had plateaued, and maintaining the weight loss benefit after semaglutide withdrawal. Discontinuation of TN-783 resulted in reversal of both weight and feeding effects, indicating that its therapeutic activity requires ongoing target engagement rather than permanent remodeling of metabolic pathways. Collectively, these observations support central NLRP3 inhibition as a distinct and promising approach for obesity treatment, offering robust induction and sustained maintenance of weight loss while preserving reversibility.

Disclosures: J.L. Guo: A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **T.P. Bachor:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **D. Braun:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **B. Huffman:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **G. Fitzgerald:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **M. Liu:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **M. Agam:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **X. Wang:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **E. Sun:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. **B. Fox:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **M. Steffek:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **T. Fischer:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **R.A. Craig II:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics. **E. Yulyaningsih:** A. Employment/Salary (full or part-time):; Tenvie Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tenvie Therapeutics.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.09/HH5

Topic: G.08. Food and Water Intake and Energy Balance

Support: NNF21OC0067317, Excellence Emerging Investigator Grant – Endocrinology and Metabolism 2021
Swedish Research Council Starting Grant 2020 (2020-02473)
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Sahlgrenska Academy (2022/334)

Title: Semaglutide effects on energy balance are mediated by Adcyap1^{+} neurons in the dorsal vagal complex

Authors: *J. TEIXIDOR DEULOFEU;
Univ. of Gothenburg, Gothenburg, Sweden

Abstract: The use of the GLP-1R agonist semaglutide is revolutionizing the treatment of obesity, yet its mechanistic effects on energy balance remain elusive. Here, we demonstrate that reactivation of semaglutide-responsive dorsal vagal complex neurons mimics the drug's effects of reducing food intake and body weight and promoting fat utilization and conditioned taste aversion. We observe that many of the semaglutide-activated area postrema (AP) and nucleus of

the solitary tract (NTS) neurons express *Adcyap1* mRNA, and ablation of AP/NTS *Adcyap1*$^+$ neurons largely reverses semaglutide's effects on energy balance acutely in lean mice and in subchronically treated obese mice. Semaglutide-activated AP/NTS *Adcyap1*$^+$ neurons promote the loss of fat rather than lean mass, with only a modest effect on conditioned taste aversion. Furthermore, NTS *Adcyap1*$^+$ neurons are engaged by GLP-1R-expressing AP neurons and are necessary for semaglutide-induced activation of several downstream satiety-related structures. Selective targeting of semaglutide-responsive *Adcyap1*$^+$ neurons holds potential for improved future anti-obesity treatments.

Disclosures: J. Teixidor Deulofeu: None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.10/HH6

Topic: G.08. Food and Water Intake and Energy Balance

Title: 24 hours Crunchometer-based feeding analysis revealed that semaglutide increases Chow preference over solid high-fat diet

Authors: *A. LOPEZ[1], E. JIMÉNEZ VALENZO[2], R. GUTIERREZ[3];
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Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as Semaglutide, are highly efficacious in treating obesity. However, the continuous microstructural dynamics of feeding behavior underlying the gradual plateau in weight loss and post-treatment rebound remain incompletely understood. To address this, we developed the Crunchometer a based computer vision pipeline to continuously track 23-h ingestive behavior at 1 Hz resolution in mice. Subjects were exposed to a competitive multi-diet environment consisting of standard Chow, High-Fat Diet (HFD), and a diverse fluid array. Mice were evaluated across three phases: Baseline, Treatment (daily subcutaneous Semaglutide vs. Saline control), and Withdrawal.We applied discrete-time Markov chain transition models, separated by circadian phases, to quantify the exact probabilities of initiating and maintaining feeding bouts alongside continuous cumulative event timelines. Our results demonstrate that Semaglutide initially drives weight loss through a profound, targeted suppression of HFD preference. Crucially, we identified a direct correlation between the gradual attenuation of weight-loss efficacy during the treatment phase and a compensatory microstructural increase in Chow consumption.Markov transition mapping mathematically corroborated this behavioral shift. As the pharmacological effect on weight loss waned, the probability of transitioning from a resting state to Chow feeding progressively increased. This compensatory Chow-rebound became strikingly evident during the withdrawal phase, where Markov matrices revealed a dominant, persistent transition drive toward Chow feeding that temporally preceded the full HFD rebound.These findings indicate that the

plateauing effect of Semaglutide-induced weight loss is driven by a distinct, compensatory rewiring of transition dynamics toward standard diet consumption, rather than a uniform failure of appetite suppression. Furthermore, our automated tracking methodology provides a scalable, high-resolution framework for phenotyping these complex, state-dependent behavioral adaptations in neuropharmacological models.

Disclosures: A. Lopez: None. **E. Jiménez Valenzo:** None. **R. Gutierrez:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.11/HH7

Topic: G.08. Food and Water Intake and Energy Balance

Title: GLP-1 Receptor Agonism Exacerbates Activity-based Anorexia in Mice

Authors: *A. THAKAR[1], T. E. BROWN[2], S. T. HENTGES[3];
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Abstract: Glucagon-like peptide-1 receptor (GLP-1R) agonists reliably reduce food intake and body weight suggesting that should be avoided in anorexia nervosa (AN). However, preclinically, these drugs reduce activity and reward seeking, key parameters of anorexia that could potentially be mitigated by GLP-1R agonists. However, this has not been systematically examined. Here, we employed a widely used rodent model of AN to determine whether a GLP-1R agonist would worsen, or rather lessen, weight loss and hyperactivity in activity-based anorexia (ABA) experiments in female mice. We employed a mild ABA paradigm where mice received 4 h/day access to chow at dark onset, continuous wheel access, and daily systemic injections of a GLP-1R agonist, antagonist, or vehicle before feeding. This model reproduced key features of the classic 2 h ABA protocol—reduced intake, anticipatory wheel running, and rapid weight loss. However, mice with 4 h daily food access increased their food intake as the paradigm continued (ABA day 0 average food intake 1.76±0.09g , ABA day 10 average food intake 3.53±0.16g, $p<0.0001$, $F_{9,9}=3.16$) and maintained their bodyweight above threshold for removal (80% of baseline) through the full 10 days of testing. Using this paradigm, we found that the GLP-1R agonist exendin$_4$ (50 µg/kg) reduced food intake relative to saline on all ABA days, whereas the antagonist exendin$_{9\text{-}39}$ did not differ from saline (mixed-effects model: day $p<0.001$, treatment $p<0.001$, interaction $p=0.005$). Total daily wheel running did not differ significantly between groups (treatment $p=0.395$), though both agonist- and antagonist-treated mice showed more food anticipatory running than saline controls. Only agonist-treated mice lost ≥20% of baseline body weight. Contrary to the hypothesis that GLP-1R agonism might attenuate ABA, agonist treatment significantly exacerbated weight loss by further suppressing intake without reducing activity. GLP-1R antagonism had no detectable effect on intake, weight, or running. These findings provide the first experimental evidence that GLP-1R agonists worsen

outcomes in an AN model, and that endogenous GLP-1 signaling does not substantially contribute to ABA pathology. These results raise caution about GLP-1R agonist use in individuals vulnerable to restrictive eating, as they are unlikely to reduce the motivation for excessive activity and can further reduce food intake.

Disclosures: A. Thakar: None. **T.E. Brown:** None. **S.T. Hentges:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.12/HH8

Topic: G.08. Food and Water Intake and Energy Balance

Support: CONICET
Agencia I+D+i
Universidad Nacional del Sur
PICT-2021-I-A-00052.
PGI 24/ZB94

Title: The metabotropic glutamate receptor MGL-2 gates satiety by modulating serotonergic signaling in C. elegans

Authors: *A. LACOUR[1,2], M. J. DE ROSA[1,2], D. H. RAYES[1,2];
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Abstract: How neural circuits encode internal nutrient states to generate adaptive behaviors is a fundamental question in neuroscience. In this study, we explore the mechanisms through which *C. elegans* perceives its nutritional state and adjusts feeding and locomotor behaviors. We show that mutants of *mgl-2*, the *C. elegans* ortholog of mammalian metabotropic glutamate receptors (mGluRs), exhibit hyperphagia and decreased locomotion—phenotypes reminiscent of hungry animals, even in the absence of food deprivation. This excessive feeding results in elevated lipid accumulation, underscoring the critical role of MGL-2 in promoting satiety.
In wild-type animals, food encounter after starvation induces a pronounced serotonin release that facilitates feeding and suppresses locomotion to promote nutrient recovery. Using genetic approaches and in vivo neuronal imaging, we demonstrate that MGL-2 is essential for the perception of nutritional status and for regulating serotonergic signaling in fed animals. Ongoing work aims to identify the specific neuronal circuits in which MGL-2 operates.
Our findings support a model in which MGL-2 acts as a key modulator within neural pathways governing appetite and energy balance. Notably, mammalian mGluRs have recently been linked to hunger and satiety perception, suggesting evolutionary conservation in these regulatory mechanisms. This study provides insights into the neurobiological basis of feeding behavior with potential relevance across species.

Disclosures: A. Lacour: None. **M.J. De Rosa:** None. **D.H. Rayes:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.13/HH9

Topic: G.08. Food and Water Intake and Energy Balance

Support: Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, NIH)

Title: Receptor-mediated activation of $G_{12/13}$ signaling in MC4R neurons exacerbates obesity in mice

Authors: *D. HASPULA[1], A. CHOI[2], O. F. GAVRILOVA[3], A. INOUE[5], J. WESS[4], S. PITTALA[4], M. RASHID[4], Z. CUI[6], Y. CUI[4], R. A. PIÑOL[7];
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Abstract: Hypothalamic melanocortin 4 receptors (MC4Rs) play a central role in regulating energy homeostasis. Stimulation of MC4R neurons strongly promotes satiety and inhibits food-seeking behavior. Together with the proopiomelanocortin (POMC) neurons, MC4R neurons form the melanocortin circuit which is critical for promoting satiety and reducing fat storage. Importantly, mutations in the *MC4R* gene have been linked to monogenic forms of obesity. MC4R neurons express many G-protein coupled receptors, several of which activate G proteins of the $G_{12/13}$ family, besides other classes of heterotrimeric G proteins. The potential metabolic relevance of $G_{12/13}$ signaling in MC4R neurons remains unexplored. To address this question, we generated mice expressing a $G_{12/13}$-coupled designer receptor ($G_{12/13}$ DREADD; $G_{12/13}$D) specifically in MC4R neurons (MC4R-$G_{12/13}$D mice). We administered deschloroclozapine (DCZ), a highly selective and pharmacologically inert DREADD agonist, via the drinking water for up to 8 weeks to $G_{12/13}$D mice and control littermates. During this time, the mice were maintained on a calorie-dense high-fat diet. DCZ-induced activation of $G_{12/13}$ signaling in MC4R-$G_{12/13}$D mice led to significant weight gain and increased adiposity. These metabolic deficits were caused by increased food intake, with no changes in energy expenditure. In line with this observation, the appetite-suppressing effects of setmelanotide, an MC4R agonist approved by the FDA for the treatment of certain types of obesity, was significantly diminished upon $G_{12/13}$ activation in MC4R neurons. In vitro biochemical studies revealed that stimulation of $G_{12/13}$ signaling in MC4R neurons greatly diminished MC4R-mediated activation of the G_s signaling cascade. Finally, we identified two GPCRs endogenously expressed by MC4R neurons, GPR183 and sphingosine-1-phosphate receptor 1 (S1P1R), that inhibited MC4R-mediated effects via activation of $G_{12/13}$ signaling. Collectively, our data indicate that stimulation of $G_{12/13}$ signaling in MC4R neurons enhances the degree of adiposity caused by the intake of a calorie-

rich diet. Clearly, our findings are of potential translational relevance. $G_{12/13}$-coupled receptors endogenously expressed by MC4R neurons may prove novel targets for the treatment of various metabolic disorders including obesity.

Disclosures: D. Haspula: None. **A. Choi:** None. **O.F. Gavrilova:** None. **A. Inoue:** None. **J. Wess:** None. **S. Pittala:** None. **M. Rashid:** None. **Z. Cui:** None. **Y. Cui:** None. **R.A. Piñol:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.14/HH10

Topic: G.08. Food and Water Intake and Energy Balance

Title: alpha-MSH-like anorexigenic Enterobacterial ClpB protein is present in the brain and is regulated by IgG

Authors: *B. THOMAS;
Univ. of Rouen Normandy, Mont Saint Aignan, France

Abstract: α-MSH-like anorexigenic Enterobacterial ClpB protein is present in the brain and is regulated by IgG Benjamin Thomas, Amaël Robert, Benjamin Lefranc, Jérôme Leprince and Sergueï O. FetissovNeuroendocrine, Endocrine and Germinal Differentiation and Communication Laboratory, Inserm UMR1239 NorDiC, University of Rouen Normandie, Rouen, 76000, France
Enterobacterial caseinolytic protease B (ClpB) has been implicated in the development of anorexia nervosa due to its mimetism with α-melanocyte-stimulating hormone (α-MSH), an anorexigenic peptide. Indeed, ClpB activates melanocortin type 4 receptor (MC4R) and stimulates production of α-MSH cross-reactive IgG playing a role of an α-MSH carrier protein in the blood. However, it remained unknown if such IgG and ClpB may reach the brain, questions that were addressed in this study. We report here that IgG induced by ClpB immunization of mice, prior to exposure to a protocol of activity-based anorexia (ABA), a model of anorexia nervosa, may be causative for ABA aggravation. Indeed, such IgG characterized by higher affinity for both ClpB and α-MSH enhanced MC4R signaling by both molecules measured by β-arrestin recruitment assay. Using specific ELISA, we also reveal that Enterobacterial ClpB is present in the brain with higher levels in the hypothalamus. Brain ClpB levels were further increased in mice developing higher affinity IgG. Moreover, these mice had also increased hypothalamic levels of ClpB-binding IgG forming immune complexes and the α-MSH peptide, independently of local POMC mRNA expression. Opposite effects, underlying protection against development of ABA, were observed in mice developing low affinity IgG which were characterized by the preferential IgG binding to the α-MSH-like epitope of ClpB. Thus, these results reveal that both ClpB protein and ClpB-binding IgG can reach the brain depending on IgG binding properties modulating ClpB and α-MSH anorexigenic signaling. These data further

clarify the putative role of Enterobacterial ClpB and of ClpB- and α-MSH-binding IgG in the pathophysiology of anorexia nervosa.

Disclosures: B. Thomas: None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.15/HH11

Topic: G.08. Food and Water Intake and Energy Balance

Support: China Postdoctoral Science Foundation 2025M772790
China Postdoctoral Science Foundation GZC20241487

Title: Development of CB1R β-Arrestin-Biased Antagonists as a Safer Therapeutic Strategy for Obesity and Metabolic Disorders

Authors: *L. XIE[1], X.-M. LI[2];
[1]Zhejiang university, Hangzhou, Zhejiang, P.R., China; [2]Inst. of Neurosci., Hangzhou, China

Abstract: First-generation CB1R antagonists (e.g., rimonabant) achieved robust weight loss but caused severe neuropsychiatric side effects attributed to broad suppression of basal CB1R signaling. We propose a revised strategy: selective suppression of β-arrestin-mediated CB1R signaling while preserving Gi tone and avoiding strong inverse agonism. Through virtual screening, structure-guided optimization, and functional validation, we identified X as a novel CB1R β-arrestin-biased negative allosteric modulator (NAM). In functional assays, X markedly suppressed β-arrestin recruitment while exerting minimal effects on Gi signaling and lacking strong inverse agonist activity. Computational modeling suggests an allosteric binding mode distinct from the orthosteric site; cryo-EM structural studies are ongoing to define the binding site and allosteric mechanism. These properties position X as a candidate to achieve metabolic benefit while avoiding the neuropsychiatric liabilities of earlier CB1R antagonists. Future work will determine the stereochemical SAR, confirm the allosteric binding site via cryo-EM, and evaluate metabolic efficacy in diet-induced obesity models using β-arrestin1/2 conditional knockout mice.

Disclosures: L. Xie: None. **X. Li:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.16/HH12

Topic: G.08. Food and Water Intake and Energy Balance

Title: Targeting Obesity and Diabetes in the CNS using Human iPSC-derived Hypothalamic Neurons

Authors: L. HARMS[1], N. MEYER[1], N. BEARDSLEY[1], L. ZEIGHAMI[2], Y. RAJ[2], K. BAKSHY[2], S. SCHACHTELE[3], C. W. MCMAHON[1], *B. FREITAS[3];
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Abstract: Glucagon-like peptide-1 receptor (GLP-1R) agonists, such as Semaglutide, have transformed the management of weight loss and type 2 diabetes (T2D). However, nausea and gastrointestinal side effects challenge patient adherence, renewing industry focus on finding secondary targets and next generation compounds that act directly on hypothalamic neurons of the central nervous system (CNS), which regulate metabolic balance and peripheral satiety signals. Of particular interest are neurons in the hypothalamic arcuate nucleus (ARC), where dysfunction is linked to metabolic disorders, including obesity, T2D, and sleep regulation. While cell lines overexpressing GLP-1R have historically supported pre-clinical research, they lack relevance for human CNS programs and cannot model dual-targeting approaches for obesity management, such as simultaneously targeting GLP-1R and gastric inhibitory polypeptide receptor (GIPR). Advances in hypothalamic neurobiology and human induced pluripotent stem cells (iPSCs) differentiation offer a new frontier for human-relevant models of CNS metabolic disorders. In this study, we report the large-scale, directed-differentiation of human iPSC-derived hypothalamic neurons and establish baseline purity, specificity, and functional profile using bulk and single-cell RNA sequencing, immunocytochemistry, flow cytometry, and GLP-1R assays. RNA sequencing confirmed expression patterns consistent with hypothalamic ARC neurons, distinct from other iPSC-derived cells, including cortical glutamatergic, GABAergic, and midbrain dopaminergic neurons. Furthermore, single-cell RNAseq data captured during differentiation confirmed progression through expected neural patterning stages for the hypothalamus. Fully differentiated hypothalamic neurons are >90% βIII-tubulin and NKX2.1-positive, with >50% POMC-positive ARC-specific neurons. To validate the model for obesity and T2D drug discovery, we confirmed POMC-positive neurons colocalization with GLP-1R. Functionally, hypothalamic neurons respond to the GLP-1R agonist, Exendin-4, showing robust dose-dependent increases in cAMP and intracellular calcium. Activation of GLP-1R was further confirmed with increased phospho-AKT detection in response to Exendin-4 stimulation, as detected by Western blot. Responses to Exendin-4 were robust and consistent across hypothalamic neurons differentiation from multiple donors. These data strongly support the quality and functionality of human iPSC-derived hypothalamic neurons as a human-relevant, high-throughput CNS model for obesity, diabetes, and metabolic disorder drug discovery.

Disclosures: L. Harms: A. Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc. **N. meyer:** A. Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc. **N. Beardsley:** A. Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc. **L. Zeighami:** A. Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc. **Y. Raj:** A. Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc. **K. Bakshy:** A. Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc. **S. Schachtele:** A. Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc. **C.W. McMahon:** A.

Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc. **B. Freitas:** A. Employment/Salary (full or part-time):; Fujifilm Cellular Dynamics, Inc.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.17/HH13

Topic: G.08. Food and Water Intake and Energy Balance

Support: 4R00DK134853-03

Title: Biochemical computation of calorie counting through hypothalamic satiety neurons

Authors: *J. BAKER, T. M. MONIZ, E. LAZEN, S. X. ZHANG;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Animals continuously adjust meal sizes according to caloric content, yet the neural computation that estimates caloric intake remains unknown. We investigated whether and how cyclic AMP (cAMP) signaling in mouse paraventricular hypothalamic MC4R-expressing neurons (PVH^{MC4R}) may enable caloric-intake estimation and calibrated meal termination. Previous work showed that feeding elevates cAMP in PVH^{MC4R} neurons through shifts in competing αMSH and NPY neuropeptide signals. Using calcium fiber photometry and two-photon cAMP imaging in behaving mice, we found that the amplitude of this peptide-to-cAMP signal scales with the caloric density of food. To test the causal role for cAMP in calorie estimation and satiation, we used an optogenetic adenylyl cyclase biPAC to artificially elevate cAMP during food intake. We found that, when animals consume low-calorie food, optogenetically boosting the cAMP signal to one typically induced by a high-calorie food caused mice to voluntarily and prematurely terminate the meal as if it is highly caloric. This cAMP elevation promotes satiation likely by scaling the excitation of PVH^{MC4R} neurons by each bite of food. Together, these findings deconstruct the circuit-molecular mechanisms through which animals use peptide-evoked cAMP signaling to represent caloric density and compute caloric intake.

Disclosures: J. Baker: None. **T.M. Moniz:** None. **E. Lazen:** None. **S.X. Zhang:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.18/HH14

Topic: G.08. Food and Water Intake and Energy Balance

Support: CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico
Universidade Federal do Rio Grande do Sul

Title: Time-Restricted Feeding Mitigates Metabolic Alterations and Modulates Appetite Control in Diet-Induced Obese Rats

Authors: *D. ENTRUDO[1,2], R. MAIA DANTAS[1,2], A. PERES[1,2], A. SILVEIRA[1,2], R. KROLOW SANTOS SILVA BAST[2];
[1]Biochimestry Dept., UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL, Porto Alegre, Brazil; [2]Biochimestry Dept., UFRGS, Porto Alegre, Brazil

Abstract: Chronic consumption of a high-fat diet (HFD) is a major driver of metabolic disordersand obesity due to disruptions in circadian feeding rhythms. Time-Restricted Feeding(TRF) has emerged as a potential intervention to realign these rhythms and mitigate HFD-induced metabolic dysregulation. This study aimed to evaluate the impact of TRF onfeeding behavior, body composition, biochemical markers, and hypothalamicinflammatory profiles in diet-induced obese (DIO) rats. All experimentais procedureswere approved by the Institutional Animal Research Ethics Committee (CEUA-UFRGS,protocol number 43150). Male Wistar rats were divided into Control (standard diet) andDIO (standard + high-fat diet) groups for 6 weeks. Subsequently, they were randomizedinto four experimental groups for a 4-week trial: CTRL-SD, DIO, CTRL-SD + TRF, andDIO + TRF. TRF groups had access to food only during their 12-hour active phase.Assessments included body weight, murinometric measurements, plasma glucose,triglycerides, cholesterol, leptin, hypothalamic inflammatory markers (IL-6, GFAP),leptin receptor immunocontent, and satiety-related feeding behavior. Data were analyzedusing a two-way repeated-measures ANOVA, with HFD and TRF as factors, followed byTukey's post-hoc test when necessary. DIO rats exhibited increased body weight,adiposity, and elevated plasma levels of glucose, triglycerides, and leptin, alongside areduction in leptin receptor immunocontent ($P<0.05$). The TRF protocol effectivelyreduced body weight, abdominal and thoracic circumference, and plasma levels ofcholesterol and leptin. Furthermore, TRF significantly decreased hypothalamic IL-6levels, as well as the immunocontent of GFAP and the leptin receptor ($P<0.05$). Whilethe satiety sequence remained intact, TRF altered activity and feeding durations ($P<0.05$).These results demonstrate that TRF, by restricting food intake to the active phase,partially reverses the deleterious metabolic and inflammatory effects of a chronic high-fat diet. Therefore, TRF serves as an efficient nutritional strategy for the prevention andmanagement of obesity.

Disclosures: D. Entrudo: None. **R. Maia Dantas:** None. **A. Peres:** None. **A. Silveira:** None. **R. Krolow Santos Silva Bast:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.19/HH15

Topic: G.08. Food and Water Intake and Energy Balance

Support: SECIHTI Grant A1-S-27322

Title: Characterization of striatal demyelination and compulsive food intake in male and female rats subjected to binge eating model during adolescence

Authors: *E. ALVAREZ[1], P. DE GORTARI[2], I. JIMÉNEZ ESTRADA[3], **J. DOLORES-SAN JUAN**[4];
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Abstract: Individuals with bulimia nervosa, who present with episodes of excessive food intake ("binge eating disorder" BE), manifest a significant decrease in white matter integrity (He et al., 2015). Transcriptomic analyses reveal that BE causes a downregulation of myelination gene expression (Kirkpatrick et al., 2017). Surprisingly, the administration of a demyelinating agent induces a reduction in binge-like eating behavior in male mice of a specific strain, but not in females (Babbs et al., 2020). This indicates that the biological mechanisms of BE are genotype- and sex-dependent. Because BE is more prevalent in adolescents, the aim of this study was to evaluate the impact of BE on striatal demyelination in juvenile rats of both sexes. Adolescent Wistar rats of both sexes were divided into 3 groups (n=12/sex): 1) control: with *ad libitum* access to standard chow, 2) intermittent access to palatable food (INT), and 3) continuous access to palatable food (CON). Food inatake, body weight and fat depots were measured. At the end of the 4-week experimental period, to analyze anxiety animals were subjected to the elevated plus maze, to measure locomotion to the gait kinematics and to the light/dark conflict test which is used to analyze compulsive food consumption. Myelin basic protein (MBP) levels were determined in the dorsal striatum (ventral and lateral regions) and in the nucleus accumbens (NAc). Body weight and visceral fat was similar between groups, while CON females had an increase in brown adipose tissue. Serum estradiol levels were unchanged in females, thus this hormone is not related to the changes observed. INT rats of both sexes developed BE and displayed compulsive food consumption, which only in females was associated with an increase in MBP expression in the NAc. INT rats had more anxiety-like behavior, regardless of sex. Locomotion similar between groups and sexes. Surprisingly, it appears that BE in females upregulates myelination in the NAc which might be activating reward and food-seeking behaviors, which can be associated with the higher prevalence of BE disorder in adolescent females.

Disclosures: E. Alvarez: None. **P. De Gortari:** None. **I. Jiménez Estrada:** None. **J. Dolores-San Juan:** None.

Poster

PSTR370: Control of Thirst, Appetite, and Energy Balance

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.20/HH16

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH K01DK143207

Title: A Gain-of-Function ANO4 Variant Causes Obesity

Authors: *L. TU;
Univ. of South Florida, Tampa, FL

Abstract: A Gain-of-Function *ANO4* Variant Causes Obesity
Authors
*Longlong Tu[1], Yong Xu[1]
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Disclosure
None.
Abstract
The rare protein-truncating *ANO4* variant is associated with higher body mass index in humans, but the causal mechanism remains unknown. Here, we generated a knock-in $Ano4^{\Delta AA}$ mouse line that recapitulates the human *ANO4* variant and develops hyperphagia and obesity. We further showed that $Ano4^{\Delta AA}$ mice exhibit an enhanced excitability of Ano4 neurons in the area postrema (AP^{Ano4}). Importantly, activation of AP^{Ano4} neurons promotes feeding without causing aversive response, which is opposed to anorexigenic AP neurons that do not express Ano4. Moreover, genetic or pharmacological inhibition of Ano4 signaling in the AP attenuates diet-induced obesity and associated hyperglycemia. Mechanistically, an Ano-specific current detected in AP^{Ano4} neurons is abolished by the *Ano4* gene deletion but is significantly enhanced by the $Ano4^{\Delta AA}$ mutation. Together, these findings establish that the human-derived *Ano4* variant is a gain-of-function mutation that drives hyperphagic obesity by potentiating the activity of orexigenic AP^{Ano4} neurons.

Disclosures: L. Tu: None.

Poster

PSTR371: Neurobiology in Changing Ecosystems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.01/HH17

Topic: G.09. Neurobiology in Changing Ecosystems

Title: Stability in Individual Behavioral Biases Differ between Drosophila Species and Serotonin Receptor Mutants

Authors: E. SILVA, M. PREDMORE, A. PORAD, P. BELL, ***R. T. MALONEY**;
Dept. of Psychology and Neurosci., Colorado Col., Colorado Springs, CO

Abstract: Individuals across a wide range of species show individual behavioral preferences even when controlling for environment and genotype. This may serve an evolutionary bet-hedging function to ensure that a fraction of the population is suited for unpredictable environment. Theoretical work has shown that the stability of these preferences within an individuals life may serve an important role in driving variation within a population, particularly for behaviors subject to selective pressures that fluctuate within an animals lifespan. We provide empirical evidence for this hypothesis by testing the stability of individual locomotor handedness across different species of *Drosophila*. We show differences between species with differing lifespans in the stability of their preferences over time, consistent with theoretical predictions for optimal bet-hedging strategies. We furthermore investigate potential mechanisms by which the stability of individual preferences could be maintained, and show that knocking out each of the five serotonin receptors in *Drosophila melanogaster* decreases the stability of individual behavioral preferences to differing degrees. Together these results provide a deeper insight into the potential ecological significance of individuality and how it may change over time, as well as provide a mechanistic substrate by which this evolutionary strategy can be implemented.

Disclosures: E. Silva: None. **M. Predmore:** None. **A. Porad:** None. **P. Bell:** None. **R.T. Maloney:** None.

Poster

PSTR371: Neurobiology in Changing Ecosystems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.02/HH18

Topic: G.09. Neurobiology in Changing Ecosystems

Support: NSF CAREER 2047331
Paul G. Allen Frontiers Group Distinguished Investigator Award in Neural Circuit Design
The Grass Foundation Fellowship
The Kavli Foundation

Title: Neurochemical and environmental modulation of decentralized cephalopod arm circuits

Authors: *G. C. WINTERS[1], R. CROOK[2];
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Abstract: Octopus arms contain decentralized peripheral circuits that support flexible sensorimotor control, yet the relationship between cellular architecture, neurochemical identity, and real-time circuit dynamics remains poorly understood. Prior HCR mapping of the *Octopus bocki* axial nerve cord (ANC) revealed abundant glutamatergic and cholinergic neurons, scattered monoaminergic and peptidergic populations, sparse GABAergic neurons, and limited

spatial segregation among many transmitter-defined cell types. Here, we tested how these distributed arm circuits respond dynamically to neurochemical and environmental perturbation. In ex vivo *O. bocki* arm slice preparations preserving ANC ganglia, muscle, suckers, and skin, we used calcium imaging to monitor spontaneous and stimulus-evoked activity during controlled application of neurotransmitters and neuromodulators. Across recordings, glutamate and dopamine acted as dominant excitatory drivers, recruiting large and overlapping ANC populations. Glutamate continued to recruit additional neurons at higher concentration, whereas dopamine responses saturated at lower dose. Serotonin was context-dependent, weakly activating networks alone but suppressing subsequent glutamate- and dopamine-driven activity when applied first. GABA and octopamine produced weak and variable effects, while high-dose acetylcholine broadly suppressed ANC activity despite inducing surrounding muscle contraction. Responsive neurons remained spatially intermingled across conditions. In parallel, ongoing calcium imaging in intact hatchling squid arms is extending this framework toward environmentally relevant perturbations in a more intact developing cephalopod preparation. Together, these data suggest that cephalopod arms rely on distributed, neurochemically diverse, and state-dependent circuit control rather than rigid anatomical partitioning of response-defined populations.

Disclosures: G.C. Winters: None. **R. Crook:** None.

Poster

PSTR371: Neurobiology in Changing Ecosystems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.03/HH19

Topic: G.09. Neurobiology in Changing Ecosystems

Support: NIH Grant R35 NS 097343
BAEF Belgium America Educational Foundation
WBI Wallonie Brussels International

Title: Temperature sensitivity of muscle fiber impedance and electrical coupling

Authors: *K. JACQUERIE[1], N. BAAS-THOMAS[3], D. J. SCHULZ[4], E. E. MARDER[2]; [1]Brandeis Univ., Boston, MA; [2]Biol., Brandeis Univ., WALTHAM, MA; [3]Brandeis Univ. Grad. Neurosci. Program, Waltham, MA; [4]Div. of Biol. Sci., Univ. of Missouri-Columbia, Columbia, MO

Abstract: The neuromuscular junction is an ideal system to study how different levels of organization interact to preserve motor function during perturbation. In the stomatogastric nervous system, previous work has shown that temperature affects motor neuron output and neuromuscular transmission, but little is known about the role of electrical coupling between muscle fibers. Electrical and dye coupling have been reported in the lobster *Homarus americanus*, suggesting that muscle fibers may not act as independent postsynaptic units. Here,

we investigated electrical coupling, impedance, and innexin expression in stomatogastric muscles of the crab *Cancer borealis*.We measured coupling between neighboring muscle fibers using two-electrode current clamp. Hyperpolarizing and depolarizing current steps were injected into one fiber while membrane voltage was recorded simultaneously from the injected fiber and an adjacent fiber. The coupling factor was calculated as the ratio at the steady state between the voltage deflection in the neighboring fiber and the voltage deflection in the injected fiber. These experiments showed that muscle fibers in gm5 and cpv4 in *Cancer borealis* are tightly electrically coupled, with an apparent coupling coefficient of 0.65. From 11°C to 20°C, apparent input resistance (R_{in}) decreased whereas coupling factor remained relatively constant (R_{in}=285 kΩ at 11°C to 229 kΩ at 20°C in gm5b, in 9 animals; R_{in}=308 kΩ at 11°C to 206 kΩ at 20°C in cpv4, in 5 animals). Coupling was similar for depolarizing and hyperpolarizing steps, indicating little or no rectification. In addition, injections with Alexa Fluor 633 hydrazide revealed dye transfer between neighboring fibers, providing anatomical support for functional coupling.To determine how coupling shapes responses to dynamic inputs, we injected ZAP currents containing frequencies from 0.1 to 30 Hz, and measured voltage responses in the injected and neighboring fibers. Apparent input impedance was frequency dependent and decreased as input frequency increased. Coupling factor also decreased with frequency, indicating that electrical coupling acts as a low-pass filter: slow voltage changes spread more effectively between fibers than fast voltage fluctuations. Finally, quantitative RT-PCR showed that gm5, gm6, and cpv1 muscles express innexin transcripts, for innexins 1-5.Together, these results show that electrical coupling is a prominent feature of stomatogastric muscles in *Cancer borealis*. Coupling may help dampen local voltage differences within a muscle and promote more uniform depolarization in response to motor neuron input.

Disclosures: K. Jacquerie: None. **N. Baas-Thomas:** None. **D.J. Schulz:** None. **E.E. Marder:** None.

Poster

PSTR371: Neurobiology in Changing Ecosystems

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Program #/Poster #: PSTR371.04/HH20

Topic: G.09. Neurobiology in Changing Ecosystems

Support: NIH Grant R90 DA060341

Title: Temperature and potassium perturbations reveal different properties of gastric and pyloric muscles of the crab, Cancer borealis

Authors: *J. M. DIMARTINO[1], K. JACQUERIE[1], A. POGHOSYAN[1], C. GUSCHLBAUER[2], E. E. MARDER[1];
[1]Biol., Brandeis Univ., Waltham, MA; [2]Animal Physiology, Inst. of Zoology, Univ. of Cologne, Köln, Germany

Abstract: The stomatogastric nervous system (STNS) of the crab, *Cancer borealis*, produces multiple behaviors on different timescales to aid in the digestion of food. Two of these behaviors are chewing, controlled by the slow (~10 sec period) gastric mill network, and filtering, controlled by the fast (~1 sec period) pyloric network. While the neural activity underlying these behaviors is well understood, the contribution of the muscles innervated by these networks to the final behavioral output is less well-studied. Here, we investigate differences in the contractile properties of the gastric mill muscle, gm6 and the pyloric muscles, cpv4/cpv6/p1, using a combination of temperature and potassium perturbations. We apply 10x [K+] saline for 40 sec to evoke contractures in both muscles simultaneously at different temperatures and measure the force output of the muscles. Gm6 exhibits greater temperature sensitivity than cpv4/cpv6/p1, with 3x stronger potentiation at 21°C but depression at 26°C which is not seen in cpv4/cpv6/p1. The dynamics of both muscles' contractures speed with increased temperatures, with Q10s of ~1.3 for both muscles across extracted metrics. Additionally, cpv4/cpv6/p1 contractures paradoxically exhibit dynamics on the order of 10s of seconds slower than gm6 contractures despite their 10x faster dynamics in vivo. We construct a biophysical model of our experiment to ask which underlying factors might result in the observed differences in contractures. The model suggests that the pyloric muscles are more completely activated by the high potassium protocol, which we confirm experimentally. Taken together, the more complete activation and resistance to depression of the pyloric muscles demonstrate differences which may allow these pyloric muscles to contract consistently in a wide range of environmental and modulatory conditions.

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Poster

PSTR371: Neurobiology in Changing Ecosystems

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Program #/Poster #: PSTR371.05/HH21

Topic: G.09. Neurobiology in Changing Ecosystems

Support: ISF 1233/23
BGU postgraduate students' scholarships

Title: A frontal cortex metabolomics study in a bipolar disorder-like mouse model as affected by exposure to ambient heat

Authors: *G. AGAM[1], A. AZAB[1], O. DAMRI[1], N. GENISH[2], I. ROSTEVANOV[1];
[1]Ben-Gurion Univ. of the Negev, Beer-Sheva, Israel; [2]Ben-Gurion Univ. of the Negev, Beer sheva, Israel

Abstract: Bipolar Disorder (BD), characterized by extreme mood oscillations between mania, euthymia, and depression, affects ~2% of the population. Its pathophysiology, although yet unresolved, is recognized as linked to mitochondrial dysfunction. Animal models are vital for

elucidating the underlying mechanisms of mental illnesses, in general, and BD, in particular. We designed a novel BD-like mouse model with construct, face and predictive validity, induced by low doses of rotenone, an inhibitor of mitochondrial respiration at complex I. Till recently, most animal and human studies avoided including females to evade theorized intricacy of feminine hormonal status. But basic and clinical practice proves frequent pathophysiological dissimilarities between the sexes. Our study's objective was to determine if mild mitochondrial dysfunction (in our BD-like mouse) combined with elevated ambient temperature induces sex-dependent frontal cortex (FC) metabolomic profile. We hypothesized that environmental heat stress, along with mild mitochondrial impairment, synergistically alter neurometabolic homeostasis in the FC and exacerbate mood-related behaviors. We also postulated that the underlying biochemical changes are sex-specific, suggesting that males and females utilize distinct metabolic pathways to cope with these physiological stressors. Our metabolomic analysis by Liquid Chromatography-Mass Spectrometry (LC-MS) of both positive and negative ionization modes lead to extensive metabolite coverage maximizing detection of diverse compound classes that ionize exclusively in a single mode. In the males Principal Component Analysis (PCA) and heatmaps indicated that while results at the manic-like state (following 4 weeks of rotenone administration) are relatively mild, the depressive-like state (following 8 weeks of rotenone administration) exhibited distinct clustering across the different paradigms. Further pathway enrichment analysis significantly pointed at purine metabolism which was verified by significant accumulation of uric acid in samples of mice exposed to combined rotenone and heat. In the females, using a similar cascade of analyses, at the depressive-like state (following 4 weeks of rotenone administration), the results indicated involvement of glutathione metabolism and taurine/hypotaurine pathways, significant elements of cellular neuroprotection. Apparently, a robust, active compensatory response is evoked, utilizing N-acetyl-1-aspartylglutamic acid (NAAG) accumulation as a cellular distress signal to counter glutathione depletion and prevent excitotoxicity.

Disclosures: G. Agam: None. **A. Azab:** None. **O. Damri:** None. **N. Genish:** None. **I. Rostevanov:** None.

Poster

PSTR371: Neurobiology in Changing Ecosystems

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Japan Society for the Promotion of Science Overseas Research Fellowship (to T.H.)
Picower Fellowship (to T.H.) by the MIT Picower Institute and the Freedom Together Foundation

Title: Discovery of new marine species Stentor hondawara and its whole-genome reveal their unique ecology in comparison with freshwater stentors

Authors: *T. HONDA[1,2,3,4], D. B. CORTES[5,2];
[1]MIT, Cambridge, MA; [2]MBL, Woods Hole, MA; [3]Broad Inst. of MIT and Harvard, Cambrdige, MA; [4]MGH and Harvard Med. Sch., Boston, MA; [5]Virginia Tech., Blacksburg, VA

Abstract: *Stentor* is a genus of large ciliates that can be found in ponds, lakes, rivers, and freshwaters all over the world. Since their initial discovery in 1744, *Stentor* strains have been isolated from all populated continents. To date, over 50 individual strains have been identified, yet not a single isolate from a marine environment has been verified. Over 200 years since the initial description of the *Stentor* genus, our study entails the first concrete discovery of a fully marine *Stentor* species, as evidenced by its morphological, ecological, and phylogenetic positioning amongst *Stentor*. This new marine organism, which we have named *Stentor hondawara*, was verified to be a new species of the *Stentor* genus that appears to have fully adapted to a uniquely marine lifestyle in a high-salinity environment. Using comparative genomics analysis between the whole-genome sequences of *Stentor hondawara* and two freshwater species of *Stentor*, we further detected several intriguing differences in the enrichment of gene orthologs between the marine *Stentor hondawara* and the freshwater species, *Stentor coeruleus* and *Stentor pyriformis*. The gene groups specifically enriched in *Stentor hondawara* encode a variety of proteins, including ion channels, pH-responsive proteins, osmoprotectants, amino acid biosynthesis enzymes, and signaling receptors. Additionally, using metagenomics, we detected and isolated, from within our initial genome assembly, the genome of a novel marine bacteria, which we propose is an endosymbiont of *Stentor hondawara*. This bacterial species is an uncharacterized member of the order *Rhodospirillales* and appears to be a nutritional factory for the host *Stentor hondawara.* Taken together, our study provides insight into how *Stentor hondawara* adapted to a marine environment distinct from the habitats of all the other currently known *Stentor* species living in freshwater.

Disclosures: T. Honda: None. **D.B. Cortes:** None.

Poster

PSTR371: Neurobiology in Changing Ecosystems

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Topic: G.09. Neurobiology in Changing Ecosystems

Support: Sigma Xi G20230315-5067
CUNY

Title: Anthropogenic noise affects acoustic behavior, auditory efferents and gene expression in the inner ear of a soniferous fish living in New York Harbor

Authors: *T. D. QUIGLEY[1], A. SKEANS[3], K. DUCLOSEL[3], X. LAZRINTH[2], P. M. FORLANO[1];
[1]Biol., [2]CUNY Brooklyn Col., Brooklyn, NY; [3]Brooklyn Col., Brooklyn, NY

Abstract: Anthropogenic noise has become common and can mask acoustic communication signals. Noise could impact the auditory efferent networks purportedly involved in gain control and signal filtering such as the cholinergic hindbrain projections to the inner ear found in all vertebrates and the central dopamine neurons which, in teleosts and mammals, project to the inner ear and have an inhibitory function on peripheral auditory sensitivity. To examine the effects of anthropogenic noise on behavior and auditory efferent systems, we studied the oyster toadfish (*Opsanus tau*) which uses acoustic communication for reproduction in New York Harbor, an area with multiple spawning locations. Using hydrophones at several of these locations, we recorded 29,868 *O. tau* advertisement calls and found that vessel noise events (n = 480) were associated with both active and diurnal call suppression. Also, the amount of noise at spawning locations varied significantly. We then asked whether fish living in areas with greater vessel noise would show differential efferent input and gene expression in the peripheral auditory system compared to fish living in quieter locations. Using immunohistochemistry, we found that choline acetyltransferase immunoreactive (ChAT-ir) puncta in the saccule, the largest end-organ of hearing in toadfish, were more numerous in fish living in relatively noisy locations. In addition, using RNAseq we examined gene expression and found that fish living in relatively loud locations had greater gene expression of KCNK1, a potassium leak channel associated with hearing sensitivity. Finally, we collected toadfish and exposed them to either field recordings of advertisement calls alone, or calls in vessel noise. In fish exposed to noise, tyrosine hydroxylase immunoreactive (TH-ir) puncta, a marker of dopaminergic input, were less numerous than in fish exposed to calls alone. Also, the area of ChAT-ir puncta was greater in noise-exposed fish. These differences suggest that teleosts may regulate behavior, gene expression and neurotransmitter production to cope with masking noise in their natural environment.

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Poster

PSTR371: Neurobiology in Changing Ecosystems

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Topic: G.09. Neurobiology in Changing Ecosystems

Support: JP21gm6110019
JPMJPR22SA

Title: Elucidation of the impact of early-life commensal microbiota colonization on brain development

Authors: *M. MIYAJIMA;
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Abstract: Birth represents a critical developmental period during which an organism initiates autonomous adaptation to the external environment, and no other stage of life involves such rapid and profound environmental change. However, the impact of early postnatal colonization by commensal microbiota on host functional development remains poorly understood. In this study, we aimed to elucidate how early-life microbial colonization influences growth, behavior, and brain functional development. By combining germ-free (GF) derivation techniques with cesarean section, we generated mice that were raised under either GF or specific pathogen-free (SPF) conditions for the first postnatal week, and analyses were performed at postnatal day 7. We first conducted behavioral assessments by evaluating ultrasonic vocalizations (USVs) at one week of age. Early postnatal germ-free (EPGF) mice exhibited a significant increase in USV frequency compared with control mice. Next, to analyze changes in neuronal activity associated with behavioral alterations, we generated early postnatal GF FosTRAP2:tdTomato mice, which enable activity-dependent neuronal labeling, and performed whole-brain imaging analyses. These experiments revealed enhanced neuronal activation in the septal hypothalamic nucleus of EPGF mice. To investigate mechanisms linking intestinal and brain alterations, we analyzed immune cell populations in the small intestine. EPGF mice showed a reduction in $CD8^+$ T cells to approximately two-thirds of the levels observed in SPF mice. In addition, comprehensive analysis of circulating immune-related molecules identified three factors, including cytokines, that were significantly altered between GF and SPF groups. Collectively, these findings suggest that early-life microbial colonization shapes intestinal immune development, alters the peripheral cytokine milieu, and thereby influences neuronal activity in specific brain regions as well as emotion-related behaviors.

Disclosures: M. Miyajima: None.

Poster

PSTR371: Neurobiology in Changing Ecosystems

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Topic: G.09. Neurobiology in Changing Ecosystems

Support: NSF Grant IOS-2444903
Texas Parks & Wildlife Gulf Coast Research Impact Grant

Title: Comparative Single-Cell Transcriptomics Reveals an Evolutionarily Ancient Homeostatic Tool Kit

Authors: *H. A. HOFMANN[1], L. SISK-HACKWORTH[1], D. A. PHOFOLOS[2];
[1]Integrative Biol., The Univ. of Texas at Austin, Austin, TX; [2]Integrative Biol., Univ. of Texas, Austin, Austin, TX

Abstract: The vertebrate hypothalamus coordinates essential physiological functions such stress response, food intake and energy balance, reproduction, osmoregulation, thermoregulation, and biological rhythms. Even though the neuroanatomical organization of the hypothalamus is variable across vertebrates, recent single-cell RNA-seq studies suggest that many of the neurosecretory cell populations such as neurons expressing corticotropin-releasing hormone, arginine vasopressin, gonadotropin-releasing hormone, proopiomelanocortin, neuropeptide Y, orexin/hypocretin, thyrotropin-releasing hormone, or molecular clock genes likely originated early in vertebrate evolution if not before. Similarly, the hypothalamus contains conserved cell populations dedicated to the regulation of context-appropriate and state-dependent social behavior, including neurons expressing EsR1 (male/female aggression), cholecystokinin A receptor (female sexual behavior), galanin (parental behavior), or nonapeptides (social approach/avoidance). However, the identification of these cell types is often based on one or few "marker genes," which may mask functional subtypes and obscure the relationships between physiological and social homeostatic networks. Moreover, the evolutionary trajectories of these cell types are poorly understood. Here, we compared in-house and publicly available hypothalamic single-nucleus RNA-seq datasets of ten jawed vertebrate species. We first identified the gene co-expression modules that characterize each homeostatic cell type across vertebrates. Specifically, we introduce a novel marker gene expression score, which, combined with unsupervised clustering and weighted gene co-expression network analysis, allows the identification of putative functional subtypes as well as pleiotropic cell populations. Next, we reconstructed the evolutionary histories of these homeostatic cell types and discovered duplication followed by divergence as a common mechanism for generating novel sub-types. Finally, we inferred patterns and rates of gene expression changes across the phylogeny to calculate genome-wide evolutionary rates and ancestral expression states for each homeostatic cell type. Our results suggest that a small set of ancient homeostatic cell types diversified by developmental duplication and evolutionary shifts in regulatory networks, thus creating the multitudes of homeostatic processes we find today. Taken together, the evolution of homeostatic regulation in vertebrates proceeded through modification of an ancestral neurosecretory toolkit rather than repeated origins of novel cell classes.

Disclosures: H.A. Hofmann: None. **L. Sisk-Hackworth:** None. **D.A. Phofolos:** None.

Poster

PSTR371: Neurobiology in Changing Ecosystems

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Program #/Poster #: PSTR371.10/HH26

Topic: G.09. Neurobiology in Changing Ecosystems

Support: Integrative Biology Recruitment Fellowship

Title: Single-Nucleus RNA-Sequencing of the Hypothalamus Reveals the Molecular Underpinnings of Physiological and Social Homeostasis Across Variable Environments

Authors: *D. PHOFOLOS[1], H. A. HOFMANN[1], S. CORNETT[1], P. WONG[1,2], T. BONNER[3], T. BONNER[4];
[1]Integrative Biol., Univ. of Texas, Austin, TX; [2]Integrative Biol., Univ. of Texas, Austin, Austin, TX; [3]Dept. of Biol., Texas State Univ., San Marcos, TX; [4]Newmarket, NH.

Abstract: Many animals experience highly variable environments, exposing them to large, and often sudden, fluctuations in temperature, precipitation, and other climatic factors that can pose a potent threat to the maintenance of physiological and social homeostasis. Still, countless species survive, and even thrive, amidst these environmental challenges. For example, males of the Plains Longear Sunfish (*Lepomis aequilensis*) form fiercely defended nesting colonies across the dramatic latitudinal temperature and longitudinal precipitation gradients of Texas. The vertebrate hypothalamus, which is central to regulating homeostasis and social behavioral, is critical for maintaining organismal homeostasis, yet the molecular and cellular mechanisms that govern how animals achieve resilience within their natural habitats are woefully understudied. To better understand and predict the strategies animals use to withstand environmental variability, here we combined climatological and hydrological data with single-nucleus RNA sequencing of the hypothalamus of reproductive *L. aequilensis* males across sites in Central Texas. We first employed machine learning to track and quantify space use and reconstruct the social networks of nest-holding *L. aequilensis* males in the wild with a video drone and discovered that spatial and social behavior is remarkably resilient in even extreme environments. We then used single-nuclei RNA-seq to examine the composition of homeostatic neuronal populations at the level of transcriptional programs. Finally, we investigated how the transcriptomes of these neurons conferred resilience within and across highly variable environments, in real time and over the course of seasons and decades. Our results uncover the homeostatic transcriptional programs that regulate social behavior, reproduction, energy homeostasis, time-keeping, stress response, temperature-sensing, and osmoregulation in the face of environmental variance across space and time.

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Poster

PSTR371: Neurobiology in Changing Ecosystems

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Topic: G.09. Neurobiology in Changing Ecosystems

Support: NIH Grant RF1-MH-118203
NIH Grant R01MH096875
NIH Grant R01AG060931

Title: Impacts of natural disaster on brain structure in rhesus macaques

Authors: *Y. YE[1], C. TESTARD[5], A. ACEVEDO-ITHIER[2], K. CHIOU[6], N. SNYDER-MACKLER[7], L. J. N. BRENT[8], M. J. MONTAGUE[2], J. SALLET[9], M. L. PLATT[2,3,4]; [2]Neurosci., [3]Psychology, [4]Marketing, [1]Univ. of Pennsylvania, Philadelphia, PA; [5]Cell. and Mol. Biol., Harvard Univ., Cambridge, MA; [6]Biol., Univ. of Alabama at Birmingham, Birmingham, AL; [7]Arizona State Univ., Phoenix, AZ; [8]Ctr. for Res. in Animal Behaviour, Univ. of Exeter, EXETER, United Kingdom; [9]INSERM / Univ. of Oxford, Oxford, United Kingdom

Abstract: Natural disasters profoundly affect human health, yet their neurobiological effects remain poorly understood despite likely contributing to resilience or vulnerability. In 2017, Hurricane Maria struck Cayo Santiago, defoliating the island and increasing heat exposure for its free-ranging rhesus macaques, creating a powerful nonhuman primate model of disaster exposure. Following the hurricane, monkeys became more affiliative and less aggressive. More affiliative monkeys were significantly more likely to survive, likely because social partners provided better access to limited shade. This natural experiment offers a unique opportunity to examine how environmental disruption and adaptive social behavior shape the primate brain.We obtained structural MRI data from adult rhesus macaques spanning both sexes and the adult lifespan in three groups: one sampled pre-hurricane (N=66) and two sampled one year (N=96) or two years (N=27) post-hurricane. Using deformation-based morphometry, we tested hurricane-related differences in gray matter volume (GMV), controlling for age, sex, and brain weight. We also tested associations between GMV and proximity, a survival-linked measure of social affiliation, while controlling for dominance rank.Post-hurricane monkeys showed larger GMV in the amygdala, anterior and posterior cingulate cortex, mid-superior temporal sulcus, and caudate ($P < 0.05$, FWE-corrected), regions implicated in social information processing. Associations between GMV and proximity were also more widespread across the brain post-hurricane than pre-hurricane, suggesting broader proximity-related neuroanatomical variation after environmental disruption. In contrast, post-hurricane monkeys showed smaller GMV in the putamen and globus pallidus ($P < 0.05$, FWE-corrected). These differences may reflect neuroplasticity in circuits supporting increased social affiliation and tolerance after habitat change, survivor effects in which monkeys with larger social-information-processing regions were more likely to survive, or both. Together, these findings provide anatomical evidence linking environmental degradation, adaptive social behavior, and the primate brain, with potential implications for resilience in humans exposed to natural disasters.

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Poster

PSTR371: Neurobiology in Changing Ecosystems

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.12/HH28

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Efectiveness of the botanical garden as a pedagogical tool to acceptance of medicinal plants

Authors: *E. RAMÍREZ MORENO[1], J. ARIAS-RICO[5], O. E. MARTÍNEZ[6], L. RIVERA-RAMIREZ[2], Z. OLGUÍN-HERNÁNDEZ[1], C. DIMAS RESENDIZ[3], Z. CALDERÓN-RAMOS[4]; [1]Univ. Autónoma del Estado de Hidalgo, Pachuca, Hidalgo, Mexico; [2]Univ. Autónoma del Estado de Hidalgo, Pachuca de Soto, Mexico; [3]Univ. Autónoma del Estado de Hidalgo, Pachuca, Mexico; [4]Univ. Autónoma del Estado de Hidalgo, SAN AGUSTIN TLAXIACA, Mexico; [5]Inst. de Ciencias de la Salud, Univ. Autonoma Del Estado De Hidalgo, Pachuca, Mexico; [6]Univ. Técnica de Machala, Machala, Ecuador

Abstract: A botanical garden is a space dedicated to the cultivation of plant species, often for scientific purposes, including research, conservation, dissemination, and preservation of living plants. These plants have been used for generations as an important alternative for maintaining or restoring health. The World Health Organization (WHO), through the efforts of a multidisciplinary team, has developed a new document entitled "WHO Traditional Medicine Strategy 2014-2023," which has spurred a renewed effort to integrate complementary medicine into public health systems. The objective of this research is to evaluate the effect of a botanical garden as an educational tool for raising awareness about the uses and benefits of traditional medicine in treating illnesses and improving the health of schoolchildren in an urban area. The methodology was based on a quasi-experimental study conducted in an urban primary school with a sample of 103 children (aged 7 to 12). The initial phase of the project comprises the design of educational materials. Phase 2 involves validating a questionnaire designed to assess the level of knowledge about the use of medicinal plants. Phase 3 comprises the implementation of an educational strategy. In the third phase, the students cultivated a botanical garden (15 species of medicinal plants) with the help of their teachers. A 15-session educational intervention was implemented to assess the impact of using the plants. The study's results include the development of an interactive digital book for children and a validated questionnaire to assess their level of knowledge about the use of medicinal plants. The result demonstrate the botanical garden, as a learning space for schoolchildren, facilited knowdledge about the ethnobotanical applications of 15 medicinal plants in several forms of application: infusions, aromatherapy. Direct contact with plants and hands-on learning in the childs promote brain functions such as attention and concentration, memory and executive functions (solving problem garden) simulate executive processes primarily controlled by the prefrontal cortex. Furthermore, identifying the uses, maintenance, and requirements of the botanical garden facilitated the recognition of the plants' vitamin content, their disease-preventive properties, and their culinary and industrial applications. This initiative also fosters the development of an educational proposal for environmental management, healthy eating, and the promotion of the garden as a space to combat obesogenic environments.

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Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

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Topic: H.05. Mood Disorders

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Title: Longitudinal single-pulse stimulation mapping reveals a network reorganization biomarker of treatment-response in depression

Authors: *N. PS[1], D. ASTUDILLO MAYA[2], K. K. SELLERS[5], J. M. FAN[6], A. TREMBLAY-MCGAW[7], N. BECKER[8], E. HAMLAT[9], A. ALLAWALA[10], V. R. RAO[3], L. P. SUGRUE[11], E. F. CHANG[4], A. D. KRYSTAL[8], A. KHAMBHATI[12];
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Abstract: Rationale: Major Depressive Disorder (MDD) involves fluctuating mood and limbic network dysfunction, with responsive neurostimulation (RNS) being explored as therapy. Biomarkers for RNS typically correlate resting brain activity with self-reported mood, which may be limited relative to active perturbation of related circuits. Single-pulse electrical stimulation (SPES) instead perturbs these networks, probing excitability and directed connectivity to yield a standardized, causal marker. To test whether SPES-evoked activity indexes depression severity, we used years-long evoked-potential mapping of network plasticity. Methods: 5 MDD patients (PRESIDIO, NCT04004169) were implanted with NeuroPace RNS with electrodes in 2 of: orbitofrontal cortex, amygdala, subgenual cingulate, ventral striatum, or nucleus accumbens. Intracranial EEG (iEEG) evoked potentials were recorded via the device (18-52 sessions/patient; up to 17.8 months) in response to 3 mA SPES with concurrent visual analog scale-depression (VAS-D) ratings. Post-stimulation waveforms (750 ms) were z-scored to

the pre-stimulation period (250 ms); root-mean-square (RMS) indexing waveform amplitude was correlated with VAS-D per stimulation-recording pair. Within each patient, iEEG waveforms from the top-correlating pair were embedded (WaveMap/UMAP) and clustered by shape (Louvain); cluster VAS-D differences were tested by one-way ANOVA against a session-level permutation null (1,000 permutations).

Results: In 4 of 5 patients, the stimulation-recording pair whose session iEEG RMS best tracked VAS-D was identified and found to be positively correlated with VAS-D ($r=0.21$-0.74; $p<0.05$). Shape analysis revealed 11-15 waveform clusters differing in concurrent VAS-D ($p<0.05$ in 4/5). Pooling waveforms across patients (3,945 waveforms), cluster VAS-D differences remained significant ($p<0.001$).

Conclusion: This study provides evidence that iEEG evoked response shape has significant potential to be a connectivity-based biomarker of long-term changes in clinical depression symptom severity.

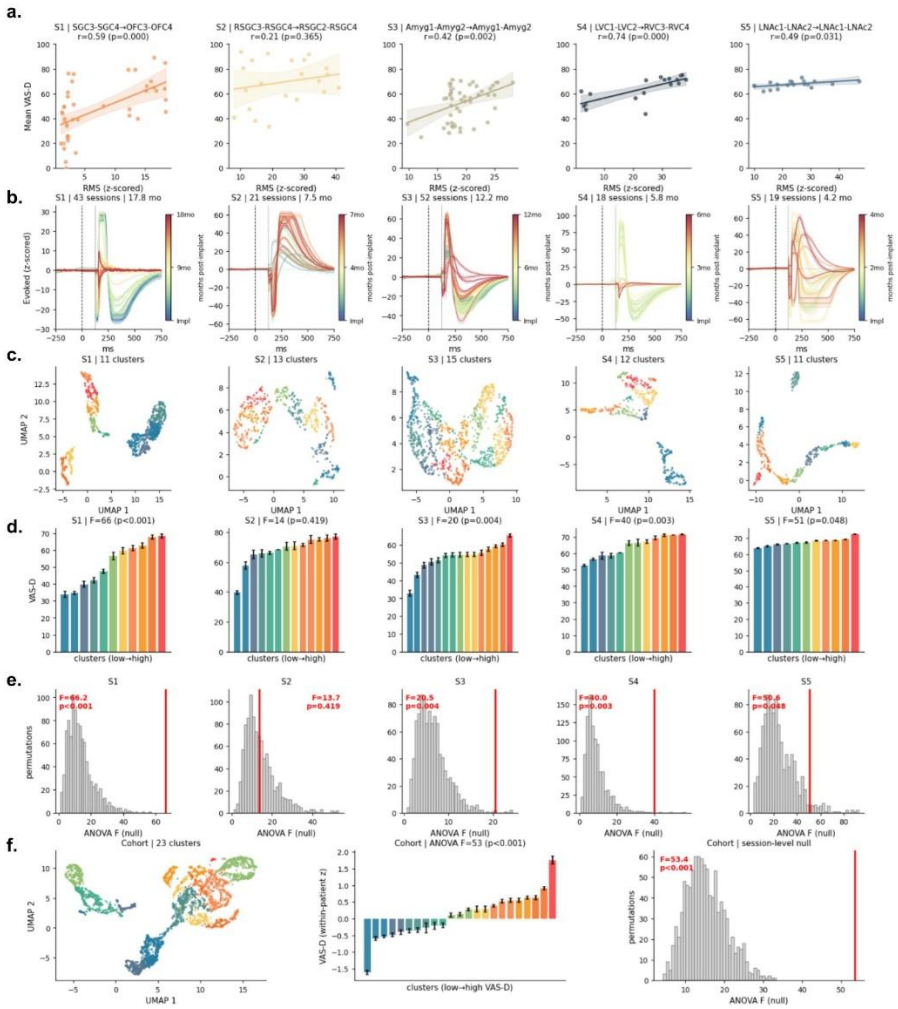


Figure 1: Evoked-potential waveform morphology tracks depression severity.
For each subject, the stim→rec pair with the strongest session-wise RMS–VAS-D correlation was selected. **a.** Pearson correlation between evoked potential (EP) waveform RMS (z-scored) and concurrent VAS-D at stimulation-recording at that pair for each patient; shading: 95% CI. **b.** EP waveform (z-scored) across sessions, colored by months post-implant (heavy dashed line: stimulation onset). **c.** WaveMap/UMAP of single-pulse waveforms from that pair, colored by Louvain cluster. **d.** Cluster mean VAS-D (±SEM), clusters ordered low→high; one-way ANOVA F with session-level permutation p. **e.** Permutation null for the ANOVA F (1,000 session-label shuffles); red line = observed F. **f.** Cohort-level (pooled best pairs, within-patient z-scored VAS-D) UMAP coloured by cluster labels, cluster mean VAS-D, and session-level permutation null.

Disclosures: N. Ps: None. **D. Astudillo Maya:** None. **K.K. Sellers:** None. **J.M. Fan:** None. **A. Tremblay-McGaw:** None. **N. Becker:** None. **E. Hamlat:** None. **A. Allawala:** None. **V.R. Rao:** None. **L.P. Sugrue:** None. **E.F. Chang:** None. **A.D. Krystal:** None. **A. Khambhati:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.02/HH30

Topic: H.05. Mood Disorders

Support: National Natural Science Foundation of China (32400914)
Multi-Year Research Grant (MYRG-GRG2025-00228-FSS)

Title: Distinct Pathways to Maladaptive Intertemporal Decision-Making in Affective Disorders: Evidence from Meta-Analysis and Systematic Review

Authors: *Y. LIN[1], L. LIU[2];
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Abstract: Maladaptive intertemporal decision-making, typically reflected in a stronger preference for immediate rewards (i.e., steeper delay discounting), has been increasingly implicated in affective disorders, including major depressive disorder (MDD) and bipolar disorder (BP). However, the factors underlying these alterations, and potentially shared versus disorder-specific neurocognitive mechanisms, remain unclear. To address this gap, we proposed an integrated cognitive-neural framework grounded in evidence from healthy populations. This framework delineated how decision-making stages (representation, valuation, choice) are supported by interactions among core cognitive functions (cognitive control, valuation, prospection) and their associated brain regions. We then conducted meta-analyses of delay discounting in clinical populations, incorporating 24 effect sizes from five MDD studies (993 participants; MDD = 688, Control = 305) and 8 effect sizes from eight BP studies (658 participants; BP = 217, Control = 273), which revealed significantly steeper delay discounting in both disorders relative to healthy controls, with additional sex-specific effects. We also conducted a systematic review of fMRI studies examining altered activity in key brain regions relevant to intertemporal choice and identified 129 studies (MDD = 82, BP = 32, Both = 15). Findings suggested disorder-related neural abnormalities: MDD was characterized by widespread regional hypoactivation and reduced functional connectivity, whereas BP showed regional hyperactivation alongside decreased connectivity. Integrating these results, we proposed a preliminary cognitive-neural framework linking neural abnormalities to cognitive dysfunctions, which may underlie maladaptive decision-making processes in MDD and BP. These findings provide mechanistic insight into intertemporal decision-making deficits in affective disorders and may inform the development of targeted interventions.

Disclosures: Y. Lin: None. **L. Liu:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR372.03/HH31

Topic: H.05. Mood Disorders

Support: ZonMw; Grant number 636320016
BBRF; Grant number 29875

Title: A randomized controlled trial investigating the effects of mindfulness-based early intervention on internalizing problems and self-referential processing in help-seeking youth

Authors: *P. LAGERWEIJ[1], M. SCHEPERS[1], A. SPECKENS[1], R. COOLS[3], G. COLLIN[2]; [2]Psychiatry, [1]Radboudumc, Nijmegen, Netherlands; [3]Radboud University, Donders Inst. (RU/DI-BCB), Nijmegen, Netherlands

Abstract: Mental health problems have increased rapidly in youth over the past two decades. Help-seeking youth (HSY) represent an early clinical stage of mental illness and a window of opportunity for early intervention. Mindfulness-based intervention (MBI) is a non-stigmatizing and transdiagnostic treatment option with established efficacy for a range of mental disorders, but its effects in early, help-seeking stages remain untested. Research on early-stage symptoms and associated neurocognitive processes are needed to establish the utility of MBI for early intervention in youth mental health. Therefore, we conducted a Randomized Controlled Trial (RCT) in HSY aged 16-25 years comparing effects of MBI + care-as-usual (CAU) with CAU-only on internalizing symptom development and self-referential processing (SRP). Assessments were conducted at baseline, end-of-treatment, 2- and 6-month follow-up. The main clinical outcome measure was the internalizing broadband scale of the Adult Self Report (ASR). At baseline and end-of-treatment, SRP was assessed using a self-referent encoding task (SRET), conducted during fMRI scanning. This task measures endorsement of and memory for positive and negative trait adjectives in three conditions: self, other, and semantic. Clinical data was analyzed on an intention-to-treat basis for N=136 participants (MBI+CAU: n=69; CAU-only: n=67) using linear-mixed effects models. Our results show that internalizing symptoms decreased more in the MBI + CAU group compared to CAU-only (Δ=-3.10, 95% CI [-5.74, -0.45], p=0.024), and group-differences further increased during follow-up (2-months follow-up: Δ=-3.79, 95% CI [-6.48, -1.10], p=0.006; 6-months follow-up: Δ=-3.94, 95% CI [-6.64, -1.23], p=0.005). SRET behavioral results indicate a stronger increase of positive self-endorsement in the MBI+CAU group compared to CAU-only (OR = 1.36, p = .026), and no significant differences for negative self-endorsement. Relative to CAU-only, the MBI+CAU group exhibited a stronger pre-to-post decrease in dorsal striatal activation during self- vs. other-referential processing (left putamen, k = 255 voxels, p-FWE < .001; right putamen, k = 91, p-FWE = .025) and for self- vs. semantic-processing in the left caudate (k = 103, p-FWE = .013). Our findings support MBI as an effective first-line intervention in HSY who present with mental health problems. SRET results show attenuation of self-positivity as an early feature of

emerging mental illness that may be amenable to MBI. Finally, neural findings suggest that early-stage MBI impacts striatal involvement in SRP, possibly indicating a beneficial influence on self-related cognitive habits.

Disclosures: P. Lagerweij: A. Employment/Salary (full or part-time):; Radboudumc / fulltime. **M. Schepers:** A. Employment/Salary (full or part-time):; Donders Institute / fulltime. **A. Speckens:** A. Employment/Salary (full or part-time):; Radboudumc / fulltime. **R. Cools:** A. Employment/Salary (full or part-time):; Donders Institute / fulltime. **G. Collin:** A. Employment/Salary (full or part-time):; Radboudumc / fulltime.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.04/HH32

Topic: H.05. Mood Disorders

Title: Single-nucleus and spatial transcriptomics of the postmortem human prefrontal cortex in bipolar disorder

Authors: *X. GUO, S. HU;
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Abstract: Bipolar disorder (BD) remains poorly understood at cellular resolution, and whether its prefrontal pathology reflects changes in cell-type abundance or transcriptional state is unclear. We profiled postmortem prefrontal cortex from 25 donors with BD and 15 non-demented control donors from the Netherlands Brain Bank, using chip-based single-nucleus transcriptomics (Stereo-cell) and spatially resolved transcriptomics (Stereo-seq). Cell-type composition did not differ detectably between groups in either cohort, localizing BD-associated changes to transcriptional state rather than to cell-type abundance. The most robust signals localized to glia and were reproducible across both platforms. Astrocytes adopted a reactive, CHI3L1-high transcriptional signature. Microglia, in contrast, downregulated their homeostatic immune-surveillance program with coordinated repression of myeloid master regulators, an immune-deactivated rather than classically activated state, alongside a HIF1A-associated metabolic shift. Spatial composition, cortical lamination and cellular-neighbourhood architecture showed no robust group differences, again pointing to state-level rather than cytoarchitectural changes. Integrating genome-wide association data, BD heritability concentrated in excitatory neurons and parvalbumin interneurons but not glia, and the genetically implicated neurons showed only small, specific changes, notably downregulated synaptic-transmission programs in inhibitory neurons. Thus genetic risk localized to neurons, whereas the most pronounced transcriptional reprogramming localized to genetically non-enriched glia. This dissociation suggests that the glial changes may be state-dependent responses rather than direct consequences of genetic risk, consistent with diminished neuronal fractalkine (CX3CL1)-microglial CX3CR1 signalling, which co-varied with microglial deactivation. Together, these convergent transcriptomic, spatial

and genetic results support a model of neuron-initiated, glia-executed pathophysiology in the bipolar prefrontal cortex.

Disclosures: X. Guo: None. **S. Hu:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.05/II1

Topic: H.05. Mood Disorders

Title: Glymphatic System Dysfunction in Major Depressive Disorder: A Systematic Review and Meta-analysis

Authors: *A. E. A. IBRAHIM[1], H. KANDIL[2];
[1]Neuropsychiatry, Alexandria Fac. of Medicine, Egypt, Alexandria, Egypt; [2]Tanta Univ. Hosp., Shebin Elkom, Egypt

Abstract: Background: The glymphatic system plays a crucial role in waste clearance within the central nervous system, and its dysfunction has been increasingly implicated in psychiatric disorders. The diffusion tensor image analysis along the perivascular space (DTI-ALPS) index serves as a novel, non-invasive neuroimaging biomarker for glymphatic activity. This systematic review and meta-analysis aimed to quantitatively evaluate glymphatic system function in patients with Major Depressive Disorder (MDD) compared to healthy controls, and to determine if age and clinical severity modulate this impairment. **Methods:** This study followed PRISMA 2020 guidelines. PubMed, Scopus, and Web of Science were systematically searched through January 31, 2026, to identify studies reporting the DTI-ALPS index in patients with major depressive disorder (MDD) and healthy controls. Two independent reviewers screened studies, extracted data, and assessed risk of bias using the Newcastle-Ottawa Scale. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were pooled using random-effects models. Leave-one-out sensitivity analyses, subgroup analyses, meta-regressions, and publication bias assessment were conducted. **Results:** Thirteen studies comprising 2,706 participants (1,628 patients with MDD and 1,078 healthy controls) were included. The pooled analysis showed a significantly lower DTI-ALPS index in patients with MDD compared with controls, indicating impaired glymphatic function (SMD = −0.48; 95% CI: −0.81 to −0.16; p = 0.003), with substantial heterogeneity (I^2 = 90.1%). Leave-one-out sensitivity analysis confirmed the robustness of the findings. Subgroup analyses identified age and depression severity as major sources of heterogeneity (p < 0.0001 for both). Glymphatic impairment was more pronounced in adults aged ≥40 years (SMD = −1.19; 95% CI: −1.49 to −0.88; I^2 = 49.9%) and in patients with moderate depression (SMD = −1.28; 95% CI: −1.67 to −0.89; I^2 = 54.5%), whereas smaller effects were observed in young adults (SMD = −0.27; 95% CI: −0.51 to −0.03), and no significant difference was found in adolescents (SMD = 0.20; 95% CI: −0.36 to 0.75). Meta-regression analyses showed that gender wasn't not significantly associated with effect size (p >

0.05). Egger's test detected no significant publication bias (p = 0.096). **Conclusion:** Glymphatic dysfunction appears to be associated with MDD and is influenced primarily by age and depression severity. Older adults and patients with moderate depression exhibited the greatest reductions in the DTI-ALPS index, while adolescent populations showed no significant alterations.

Disclosures: A.E.A. Ibrahim: None. **H. Kandil:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.06/II2

Topic: H.05. Mood Disorders

Support: NIH Grant R01HD097619
NIH Grant R56MH113627
NIH Grant R01MH119086

Title: Dissociable Motor and Perceptual Alterations of Physical Effort in Major Depressive Disorder

Authors: *V. LOOI[1,3], G. E. STEWARD[2,3], V. S. CHIB[2,3,4];
[2]Biomed. Engin., [1]Johns Hopkins Sch. of Med., Baltimore, MD; [3]Kennedy Krieger Inst., Baltimore, MD; [4]Kavli Neurosci. Discovery Institute, Johns Hopkins Univ., Baltimore, MD

Abstract: Motivational impairment is a core feature of Major Depressive Disorder (MDD), yet the mechanisms linking depressive symptoms to reduced willingness to engage in effortful behavior remain unclear. Effort-based decision-making paradigms often confound perceived effort costs with reward valuation, making it difficult to isolate alterations in effort perception itself. Here, we examined subjective effort perception during physical exertion by dissociating objective force production from retrospective effort assessment.
Thirty participants with MDD (mean age = 22.9 years, SD = 4.6; 6 male, 24 female) and 31 healthy controls (mean age = 24.8 years, SD = 4.8; 9 male, 22 female) completed a grip-force task using a hand dynamometer. Following calibration and training, participants exerted force to fill a visual bar without explicit effort targets and subsequently rated the perceived effort associated with each exertion. For each trial, we quantified mean exertion (ME), exertion variability (EV), and assessment error (AE), defined as the discrepancy between perceived effort and actual force output. Linear mixed-effects models were used to evaluate group differences and symptom associations.
Despite producing comparable levels of force, participants with MDD exhibited greater exertion variability than healthy controls (p = .033), even after accounting for mean exertion. They also consistently perceived their exertions as more effortful than both the intended effort goals and the ratings of healthy controls (p = .004). To determine whether this inflation reflected

differences in motor performance, we modeled AE as a function of EV normalized by ME (EVN). Although higher EVN predicted larger AE across participants ($p = .009$), a significant effect of MDD remained ($p = .020$), indicating that elevated effort assessments in depression cannot be fully explained by greater motor variability.
Within the MDD group, greater depressive symptom severity ($p < .001$) and fatigue severity ($p < .001$) were associated with reduced force exertion, whereas depressive symptom severity selectively predicted greater EV ($p = .047$) and EVN ($p = .002$).
Together, these findings suggest that physical effort is altered at two dissociable levels in MDD: motor output is less stable, and subjective effort is systematically inflated beyond what can be explained by motor variability or symptom severity. This persistent overestimation points to an altered mapping between motor output and effort perception, potentially increasing the subjective cost of exertion and contributing to motivational impairments in depression.

Disclosures: V. Looi: None. **G.E. Steward:** None. **V.S. Chib:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.07/II3

Topic: H.05. Mood Disorders

Title: Examining neural activation in bipolar I disorder during mania: A meta-analysis of functional magnetic resonance imaging studies.

Authors: *A. SANCHEZ VIRRUETA[1], S. HERRERA[2], F. AMAYA REYES[5], G. JOHNSON-VENEGAS[3], C. BATEN[6], G. ZAMORA[7], E. WOO[1], D. HEDGES[8], C. MILLER[4];
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Abstract: Examining neural activation in bipolar I disorder during mania: A meta-analysis of functional magnetic resonance imaging studies.Ariana Sanchez Virrueta1, Summer Herrera1, Fabiola Amaya Reyes1, Gabrielle Johnson-Venegas1, Caitlin Baten1, Gladys Zamora1, Patrick Durkee, Ph.D.,1 Ellen Woo, Ph.D.,1 Dawson Hedges, M.D.,2 Chris Miller, Ph.D.1
1California State University, Fresno, 2Brigham Young University
Introduction: Bipolar I disorder (BD-I) is an affective disorder characterized by cycles of recurrent manic and major depressive episodes. Functional magnetic resonance imaging (fMRI) studies have identified neural differences between bipolar disorder and healthy controls. However, many of these studies have reported inconsistent or even conflicting findings.
Objectives: By limiting the analysis to BD-I during active mania, this meta-analysis aims to advance our understanding of the neural underpinnings of active mania only and not euthymic or

depressive states in BD-I compared to healthy controls.
Methods: We conducted a comprehensive literature screening on PubMed (N = 512) to gather primary studies that met predefined inclusion criteria. Eleven task-based primary studies were selected, and whole-brain voxelwise brain coordinates were extracted. All articles were independently screened by two coding teams following PRISMA guidelines. A total of 47 peak activations were analyzed using multilevel kernel density analysis (MKDA) with ensemble thresholding ($p < 0.05$ to 0.0001) to reduce cluster size bias. Statistical significance was assessed using 10,000 Monte Carlo simulations to control for family-wise error (FWE).
Results: No clusters survived FWE correction. However, several subthreshold trends were observed such as hypoactivation in the left rectal gyrus (4, -50, -16).
Conclusions: These findings suggest that the current literature on fMRI task-based studies investigating mania are too sparse to warrant any robust conclusions. Additional studies are needed to better characterize the neural correlates of mania in BD-I.

Disclosures: A. Sanchez Virrueta: None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.08/II4

Topic: H.05. Mood Disorders

Title: Decoding Treatment-Resistant Depression: Neural Biomarkers of Brain Network Temporal Directionality and Response to Repetitive Transcranial Magnetic Stimulation

Authors: *Y. SHIH[1], C. HSU[2], C.-P. LIN[2,3], L.-H. CHANG[2];
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Abstract: Treatment-resistant depression (TRD) is increasingly conceptualized as a disorder of disrupted coordination across brain networks supporting cognitive control, salience detection, and emotional processing. Although repetitive transcranial magnetic stimulation (rTMS) has become an established intervention for TRD, its system-level neural mechanisms remain incompletely understood. Most neuroimaging studies have focused on prefrontal stimulation targets and static functional connectivity, offering limited insight into the consistent, large-scale network changes associated with neuromodulation. We applied activation likelihood estimation (ALE) meta-analysis and meta-analytic connectivity modeling (MACM) to characterize the network basis of TMS-related neuroimaging findings across major depressive disorder (MDD) and TRD. A systematic literature search was conducted in PubMed and other databases following PRISMA guidelines, and included coordinates reflecting TMS-related activation or connectivity changes. Coordinate-based meta-analysis was performed in GingerALE 3.0.2 using cluster-level family-wise error correction ($p < 0.05$; cluster-forming threshold $p < 0.001$). In

total, 33 experiments comprising 135 foci from 14 studies were included. Significant ALE clusters served as seed regions for MACM, and whole-brain co-activation patterns were derived from the BrainMap database. ALE revealed two regions of consistent TMS-related involvement: the right precentral gyrus (Brodmann area 6) and the left claustrum. MACM showed that the right precentral seed co-activated predominantly with the supplementary motor area, premotor cortex, and parietal regions, consistent with a sensorimotor and dorsal-attention network. By contrast, the left claustrum co-activated broadly with the insula, anterior cingulate cortex, postcentral gyrus, and cerebellum, suggesting involvement in salience-related and multimodal integrative circuits. These findings indicate that the neural correlates of TMS in depression extend beyond the canonical dorsolateral prefrontal target to encompass distributed networks. The claustrum-anchored, salience-related architecture in particular may represent a system-level substrate relevant to emotional dysregulation and treatment response. Given the small size of the claustrum and its proximity to the insula, this localization warrants cautious interpretation. This work offers a network-based framework to guide future studies of directed connectivity, individualized neuromodulation, and treatment-response biomarkers.

Disclosures: Y. Shih: None. **C. Hsu:** None. **C. Lin:** None. **L. Chang:** None.

Poster

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Program #/Poster #: PSTR372.09/II5

Topic: H.05. Mood Disorders

Support: NIMH R21 MH126197-01A1

Title: Altered learning drives decisional reference point elevation in major depressive disorder

Authors: *A. VITTALA[1], K. LOUIE[2], C. M. RAIO[3], D. IOSIFESCU[3], P. W. GLIMCHER[2]; [2]Dept. of Neurosci., [3]Dept. of Psychiatry, [1]NYU Langone, New York, NY

Abstract: We recently showed that the decisional reference point, which defines the border between positive and negative reinforcement, is pathologically elevated in major depressive disorder (MDD) and strongly correlated with depression severity (Vittala et al., PNAS, 2026). We measured the reference point using a foraging task where participants must balance immediate rewards against the opportunity cost of time, which is formally defined as the reference point (Constantino & Daw, 2015). The Marginal Value Theorem (MVT) provides a mathematical formula for calculating the optimal reference point in foraging. Relative to this optimal, we found that patients with MDD tend to underharvest while healthy controls tend to overharvest.
The computational mechanism underlying both patterns remain unclear, and a better understanding of this mechanistic difference may provide insight into the underlying neural computation differences in MDD. Here, we used computational modeling in our previously

published dataset to assess whether abnormal reference point setting in patients with MDD reflects altered temporal discounting, a skewed learning process, or changes in utility curvature. To test this hypothesis, we fit a family of reinforcement-learning and MVT-based models to the foraging behavior of healthy controls and patients with MDD. We found that altered temporal discounting in model-free reinforcement learning could not explain the underharvesting observed in MDD, while MVT-based learning models better captured observed behavior as measured by Akaike information criterion.
In participants with MDD, a learning model which incorporates differential updating for positive and negative prediction errors best accounted for our data. This suggests that MDD may reflect a specific pathology of the mechanism for reference point learning rather than altered utility curvature or changes in time discounting.

Disclosures: A. Vittala: None. **K. Louie:** None. **C.M. Raio:** None. **D. Iosifescu:** None. **P.W. Glimcher:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.10/II6

Topic: H.05. Mood Disorders

Support: NIH UH3NS103549
R01MH1340597
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Robert and Janice McNair Foundation

Title: Conserved Fiber Topography of the Anterior Limb of the Internal Capsule in Treatment-Resistant Psychiatric Patients

Authors: *R. EL JAMMAL[1], H. SUZUKI[2], L. S. MATTAR[1], T. HAMRE[1], S. SOUBRA[1], M. A. RYAN[1], R. K. MATHURA[1], S. J. MATHEW[3], A. ALLAWALA[7], E. A. STORCH[4], N. VANEGAS-ARROYAVE[2], G. P. BANKS[1], N. POURATIAN[8], R. PATRIAT[9], W. K. GOODMAN[5], N. R. PROVENZA[1], S. A. SHETH[1], E. BARTOLI[6], S. R. HEILBRONNER[1]; [1]Neurosurg., [2]Neurol., [3]Psychiatry, [4]Psychiatry & Behavioral Sci., Baylor Col. of Med., Houston, TX; [5]Psychiatry, Baylor Col. of Med., Bethesda, MD; [6]Dept. of Neurosurg., Baylor Col. of Med., Houston, TX; [7]Neurosurg., Univ. of California San Francisco, San Francisco, CA; [8]Neurolog. surgery, Southwestern Med. Ctr., Dallas, TX; [9]CMRR / Radiology, Univ. of Minnesota, Minneapolis, MN

Abstract: The anterior limb of the internal capsule (ALIC) connects prefrontal cortical (PFC) regions to the thalamus, brainstem, and subthalamic nucleus. Structural and functional abnormalities within the ALIC circuit have been associated with many neuropsychiatric disorders, including obsessive-compulsive disorder (OCD) and depression, and DBS may

provide relief to treatment-resistant patients. However, it remains unclear whether the well-characterized topographic organization of the prefrontal-subcortical pathways within the ALIC is preserved in treatment-resistant psychiatric populations in which this circuit is implicated in disease pathophysiology.We reconstructed PFC-subcortical pathways using diffusion tractography and quantified their spatial organization within the ALIC in treatment-resistant OCD (n=18) and depression (n=5) patients which was evaluated using Wilcoxon signed-rank tests (dorsal vs central vs ventral fiber positions). In depression patients, we also evaluated ALIC topography using cerebro-cerebral evoked potentials (CCEPs) elicited by single-pulse electrical stimulation of DBS leads in the ALIC and recordings in the orbitofrontal cortex (OFC). Diffusion tractography results revealed a conserved dorsoventral organization of PFC fibers and a mediolateral organization of subcortical pathways within the ALIC among treatment-resistant psychiatric patients, with dorsal, central, and ventral fiber groups occupying significantly distinct spatial positions (all $p<0.05$), consistent with patterns observed in healthy individuals and preclinical models. CCEP recordings in the OFC demonstrated a significant relationship between stimulation contact location and OFC response, whereby ventral ALIC stimulation preferentially engages medial OFC contacts and dorsal ALIC stimulation engage lateral OFC response pattern only in the left hemisphere ($p=0.049$). Our findings confirm that topographic patterns within the ALIC previously identified using preclinical models and healthy controls are preserved in treatment-resistant psychiatric patients. Furthermore, stimulation-evoked cortical responses exhibit organization consistent with the structural architecture, linking white matter topography to functional network engagement in humans that supports more precise and individualized neuromodulatory strategies for neuropsychiatric disorders.

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Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.11/II7

Topic: H.05. Mood Disorders

Title: The utility of event-related brain potentials as biomarkers for depression and anxiety in college students

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[1]Psychology, North Carolina Agr. and Tech. State Univ., Greensboro, NC; [2]Psychology, North Carolina A&T State Univ., Greensboro, NC

Abstract: Anxiety and depression are major mental health issues facing college students. The search for mental health biomarkers is a challenge. An event-related brain potential (ERP) is the brain's bioelectric response to stimuli. The mismatch negativity (MMN) is an ERP reflecting the pre-attentive automatic detection of auditory changes. The MMN is generated in the auditory cortex and is associated with glutamate, dopamine, and serotonin. The pattern-reversal visual evoked potential (PREP) reflects activity from the retina to the striate cortex, as it is elicited from a reversing checkerboard pattern. The PREP is generated in the striate cortex and is associated with glutamate, GABA, and acetylcholine. The late positive component (LPC) is an ERP that reflects the brain's activity to stimulus evaluation, working memory, and to emotional stimuli as it is produced when individuals view pictures, words, or hear sounds. The LPC is generated in the hippocampus and is associated with norepinephrine, dopamine, and acetylcholine. Fifteen college students were participants. We evaluated the following hypotheses: (1) The MMN deviant amplitude and PREP P100 latency will be associated with anxiety and depression. (2) The LPC latency of task-specific differences will be associated with anxiety and depression. Eight scalp electrodes (Fz, Cz, Pz, C3, C4, P3, P4, Oz) were used and all referenced to linked earlobes. To elicit the MMN, participants listened to 400 random tones (80% standard, 20% deviant). For the PREP, they watched a checker-board pattern reverse 100 times from black to white squares. During the LPC task, to elicit working memory, participants used a game controller to select target and non-target letters, while forming two-letter words. The statistically significant results follow. The MMN deviant amplitude was significantly more negative for higher anxiety and depression scores. The PREP P100 latency was significantly longer for higher anxiety scores. The LPC latency revealed higher task-specific differences at the Cz electrode predicting lower anxiety scores. Given the known generators and neurotransmitters, these results indicate that the MMN, PREP, and LPC can potentially be used as non-invasive biomarkers for anxiety and depression in college students.

Disclosures: G.S. Robinson: None. **K. Harper:** None. **A. Briggs:** None. **T. Sheppard:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR372.12/II8

Topic: H.05. Mood Disorders

Support: Shanghai Municipal Science and Technology Major Project 2018SHZDZX01

Title: The ventromedial prefrontal cortex and lateral orbitofrontal cortex in emotion and depression

Authors: *E. T. ROLLS[1], Y. CHEN[2];
[1]Oxford Ctr. For Computat. Neurosci., Coventry, United Kingdom; [2]ISTBI, Fudan Univ., Shanghai, China

Abstract: The orbitofrontal cortex is the key cortical region involved in emotion and subjectively reported emotions in humans (Rolls 2026a,b). Here we extend the analysis of emotion to depression and the ventromedial prefrontal cortex (vmPFC). We measured functional connectivity in 175 patients with not yet treated first episode major depressive disorder with a mean age of 22 years, and 239 healthy controls (HC) using the Human Connectome Project Multimodal Parcellation of the brain (Rolls et al 2026).
Reduced resting state functional connectivity was found in depression of ventromedial prefrontal cortex (vmPFC) regions closely related to the medial orbitofrontal cortex implicated in reward with the medial temporal lobe / hippocampal memory system, and with somatosensory cortical areas, especially in the right hemisphere. The locations of these reduced functional connectivities of vmPFC regions in depression were confirmed in a voxel-level analysis, and were associated with the depression symptoms of reduced libido (Hamilton Depression Rating Scale HAMD14) and insomnia (HAMD4). The lateral orbitofrontal cortex regions (47m, 47s, 47l, a47r, and p47r, implicated in punishment and non-reward) had functional connectivities with other cortical regions that were positively correlated with General Somatic Symptoms (Hamilton depression subscale HAMD13 (heaviness in the limbs, back or head; backaches, headaches, muscle aches; loss of energy and fatigability); sadness (Beck Depression inventory BDIA); guilt (BDIE), and punishment (BDIF); implicating the lateral orbitofrontal cortex in these key symptoms of depression.
The results extend our understanding of depression by demonstrating reduced functional connectivity of the vmPFC in depression relating to reduced motivation, and that the lateral orbitofrontal cortex punishment and non-reward system has connectivity associated with unpleasant somatic symptoms and sadness. Implications include the need for new treatments to increase the functional connectivity of the vmPFC as well as medial orbitofrontal cortex, which are not treated by conventional antidepressants such as selective serotonin reuptake inhibitors.
Rolls, E. T. (2026a). Brain Computations and Principles; and AI. Oxford University Press, Open Access, Oxford.
Rolls, E. T. (2026b). Neuroscience Discoveries. MIT Press, Open Access, Cambridge, MA.
Rolls,E.T., Chen,Y., Cheng,W., Luo,Q., Wang,X., Zhang,T. and Feng,J. (2026b). The ventromedial prefrontal cortex and lateral orbitofrontal cortex in depression (in review).

Disclosures: E.T. Rolls: None. **Y. Chen:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR372.13/II9

Topic: H.05. Mood Disorders

Support: NIMH Grant K01 MH128663

Title: Early Slow-Wave Sleep Gains as a Marker of Antidepressant Response During Electroconvulsive Therapy

Authors: *R. GREENSPAN[1], L. LEBOVITZ[2], B. A. PALANCA[1,2,3,4,5], N. B. FARBER[2], M. KAFASHAN[1,2,4];
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Abstract: Electroconvulsive therapy (ECT) is an established and highly effective treatment for patients with severe depression. However, its mechanisms of action remain incompletely understood, and objective early markers of antidepressant response are still needed. Slow-wave sleep (SWS) plays an important role in synaptic plasticity that may be relevant to antidepressant recovery. We examined whether early changes in SWS during ECT were associated with changes in depression severity. Twenty-two participants undergoing an index course of ECT in an ongoing longitudinal study, DNS-ECT, ClinicalTrials.gov NCT05905705, completed overnight sleep EEG recordings and Montgomery-Åsberg Depression Rating Scale (MADRS) assessments over the course of therapy. We examined whether early change in SWS, measured from baseline to two weeks after ECT initiation as a percentage of total sleep time, was associated with change in depression severity from baseline to the end of the ECT course. To account for potential heterogeneity in treatment response, we used a two-component Gaussian mixture model to identify latent response phenotypes based on changes in SWS and MADRS scores. Within each phenotype, we assessed the association between SWS change and MADRS change using Pearson and Spearman correlations. We then used multiple linear regression to test whether the association between SWS change and MADRS change differed by phenotype. MADRS scores decreased substantially by the end of the ECT course, with a mean reduction of 14.1 points from baseline (paired $t = 7.30$, $p < 0.0001$). Mean (SD) SWS increased from 60.0 (54.8) to 83.8 (82.6) minutes ($\Delta = +24.3$ minutes, +6.2 %) from baseline to week 2. The mixture model identified two response phenotypes of similar size ($n = 12$ and $n = 10$) that did not differ at baseline in age, sex, MADRS, QIDS, or SWS (all $p > 0.30$). Within both phenotypes, greater SWS gains were strongly associated with greater MADRS reductions. Phenotype 1 showed a slope of −0.92, Pearson $r = −0.86$, $p = 0.0004$; phenotype 2 showed a slope of −0.44, Pearson $r = −0.85$, $p = 0.002$. The combined model explained 79% of the variance in MADRS change

(overall $p < 0.0001$). Phenotypes differed in coupling magnitude but not direction (interaction $p = 0.024$; likelihood-ratio $p = 0.012$). Early gains in SWS during the first two weeks of ECT were closely coupled to subsequent reductions in depression severity assessed at the end of the ECT course across two latent response phenotypes, supporting a consistent relationship between SWS enhancement and antidepressant response. Larger studies are needed to replicate these findings and identify prospective markers of phenotype membership.

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Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.14/II10

Topic: H.05. Mood Disorders

Title: Effectiveness of AI and Rule-Based Conversational Agents for Depression, Anxiety and Stress: A Meta-Analysis

Authors: S. MOKHTARI MASOUMI ALAMDARLOO[1], ***A. MIRZAKHANI**[2], M. AZHDARLOO[1], E. HAGHANI-SAMANI[2], A. NAZARI[3];
[1]Shiraz Univ., Shiraz, Iran, Islamic Republic of; [2]Tehran Univ. of Med. Sci., Tehran, Iran, Islamic Republic of; [3]Shahrekord Univ. of Med. Sci., Shahrekord, Iran, Islamic Republic of

Abstract: Depression, anxiety, and stress are significant global health burdens worsened by restricted access to care. Conversational agents (CAs), encompassing both AI(Artificial Intelligence)- and rule-based systems, provide scalable mental health interventions. This systematic review and meta-analysis analyzed the efficacy of CA interventions in 48 randomized controlled trials covering 28,071 participants. It demonstrated small-to-moderate but significant effects in minimizing symptoms of depression (SMD: −0.27), anxiety (SMD: −0.20), and stress (SMD: −0.26). A Robust Variance Estimation (RVE) approach was used to address within-study dependencies, with results consistent with the random-effects model. Subgroup analyses investigated sources of heterogeneity and indicated greater effects in clinical populations and shorter-duration interventions. Meta-regression identified no appreciable effect of outcome timing. Risk of bias was largely low, although some studies had issues due to missing data or selective reporting. Publication bias was negligible. These results provide evidence for the utilization of conversational agents as effective interventions for lessening psychological symptoms. Additional research is required to evaluate their long-term effectiveness and how best to integrate them into mental healthcare systems

Disclosures: S. Mokhtari Masoumi Alamdarloo: None. **A. Mirzakhani:** None. **M. Azhdarloo:** None. **E. Haghani-Samani:** None. **A. Nazari:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.15/II11

Topic: H.05. Mood Disorders

Title: Childhood Adversity, Depression, and Sleep Disturbance Independently Predict Suicide Risk in Medical Students: Evidence for a Neurodevelopmental Vulnerability Pathway

Authors: *D. P. GUÍZAR;
Univ. Nacional Autónoma De México, Ciudad de México, Mexico

Abstract: Early-life adversity has been associated with long-term alterations in stress-response systems, emotional regulation, sleep architecture, and vulnerability to psychopathology. Suicide risk is highly prevalent among medical students; however, the relative contribution of childhood maltreatment, depressive symptoms, anxiety, and sleep disturbances remains insufficiently understood. We examined independent factors associated with suicide risk within a neurodevelopmental vulnerability framework.A cross-sectional analytical study was conducted in 673 second-year medical students (69.4% women; mean age = 20.0 ± 1.3 years) from the National Autonomous University of Mexico. Participants completed validated self-report measures assessing depressive symptoms (Patient Health Questionnaire-9), anxiety (Generalized Anxiety Disorder-7), academic stress (SISCO Inventory), sleep quality (Pittsburgh Sleep Quality Index), childhood adversity (Childhood Trauma Questionnaire), and suicide risk (Plutchik Suicide Risk Scale). Logistic regression analyses were performed to identify independent predictors of suicide risk while controlling for sex and relevant psychological variables.Mental health problems were highly prevalent. Moderate-to-severe depressive symptoms were observed in 46.6% of participants, moderate-to-severe anxiety in 33.9%, poor sleep quality in 79.9%, and clinically relevant suicide risk in 26.0%. Correlation analyses revealed strong associations between depressive symptoms and anxiety ($\rho = 0.74$), and between depressive symptoms and suicide risk ($\rho = 0.70$). Poor sleep quality was significantly associated with depression, anxiety, and suicide risk. Students with suicide risk showed substantially higher rates of depression (84.6% vs. 32.9%), anxiety (65.7% vs. 22.3%), academic stress, and childhood emotional abuse.In multivariable logistic regression models, childhood abuse remained the strongest independent predictor of suicide risk (OR = 1.26, 95% CI: 1.14–1.40, $p < 0.001$). Depressive symptoms also independently predicted suicide risk (OR = 1.22, 95% CI: 1.15–1.29, $p < 0.001$), followed by poor sleep quality (OR = 1.14, 95% CI: 1.05–1.24, $p = 0.003$). Anxiety, childhood neglect, and sex were not significant after adjustment.These findings support a neurodevelopmental vulnerability pathway in which early-life adversity contributes to later suicide risk through persistent emotional and sleep-related dysregulation. Childhood abuse, depression, and sleep disturbance emerged as key targets for early identification and preventive interventions in vulnerable young adults.

Disclosures: D.P. Guízar: None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.16/II12

Topic: H.05. Mood Disorders

Support: National Key R&D Program of China (No. 2021YFC2501400)

Title: Spatiotemporal Dynamics of Emotion Processing Brain Networks in Insomnia and Comorbid Emotional Disorders: A Simultaneous EEG-fMRI Study

Authors: *Y. GENG[1], P. WU[1,2];
[1]Dept. of Neurobiology, Sch. of Basic Med. Sciences, Natl. Inst. on Drug Dependence, Peking Univ., Beijing, China; [2]Beijing Key Lab. of Innovative Intervention Techniques and Translational Res. for Mental Disorders Rehabil., Beijing, China

Abstract: Background: Insomnia disorder (ID) is highly comorbid with depression and anxiety, sharing core vulnerabilities in aberrant emotional processing. However, the neurobiological mechanisms distinguishing pure insomnia from emotional comorbidities remain unclear. This study utilizes simultaneous EEG-fMRI to elucidate how emotional processing and regulation networks are differentially disrupted. Methods: Participants-including healthy controls (HC, n=29), pure insomnia (INS, n=23), and insomnia with comorbid emotional disorders (INS+EMO, n=32)-underwent simultaneous EEG-fMRI recording during passive facial emotion recognition and active emotion regulation tasks. Behavioral metrics (accuracy, intensity ratings, reaction times) and whole-brain mean amplitude of low-frequency fluctuations (mALFF) were evaluated as the primary neuroimaging profiles underpinning the subsequent electrophysiological state decoding. Results: Distinct pathognomonic dissociations emerged between clinical sub-types. During facial recognition, the INS group exhibited emotional blunting (reduced sensitivity to negative valence), whereas the INS+EMO group displayed valence inversion and a hyperarousal bias toward neutral stimuli. Furthermore, INS patients showed accuracy-specific deficits, while INS+EMO patients suffered dual impairments in both accuracy and cognitive efficiency (global reaction-time slowing). During emotion regulation, the INS group demonstrated diminished regulatory capacity, whereas the INS+EMO group manifested severe systemic disorganization characterized by highly stochastic decision-making and a profound loss of task-evoked reaction time flexibility(state-rigidity). Neurally, functional mapping revealed a significant, progressive stepwise increase in bilateral precuneus mALFF across cohorts (HC < INS < INS+EMO). Conclusion: This study provides compelling behavioral and neural evidence of a dissociation between pure insomnia and its emotional comorbidities. The stepwise overactivation of the bilateral precuneus highlights its potential as a neuroimaging biomarker for circuit-level hyperarousal and top-down emotional dysregulation, offering a framework for targeted circuit-based interventions.

Disclosures: Y. Geng: None. **P. Wu:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.17/II13

Topic: H.05. Mood Disorders

Title: Resting-state fMRI entropy is heterogenous across major depressive disorder and is linked to clinical trajectories

Authors: *S. J. LYONS[1], I. BECK[2], J. FOLEY[1], B. E. DEPUE[1];
[1]Univ. of Louisville, Louisville, KY; [2]Arizona State Univ., Mesa, AZ

Abstract: Major depressive disorder (MDD) is one of the leading causes of disability worldwide. Decades of research have targeted potential neurobiological mechanisms of MDD, yet investigations predominately overlook two major considerations. MDD is a heterogeneous disorder which complicates the identification of neurobiological markers. Additionally, many investigations do not explicitly consider the variability of neural function despite its strong association with underlying biological systems. Therefore, we investigated the complexity of resting state MRI activity using multiscale sample entropy to explore the heterogeneity of functional complexity and its relationship with clinical factors. Post-processed and filtered data were provided by the *Depression Imaging Research Consortium*. A total of 1,650 participants with MDD were included in the final analysis. Gaussian mixture models (GMM) were performed for each sample entropy scale. We identified 3 subgroups as the most stable solution, exhibiting excellent classification stability. Subgroups were distinguished by global rather than regional differences, typified by high, moderate, or low entropy. Pairwise Mann-Whitney U and logistic regression analyses were performed to identify clinical differences between subgroups for each scale using Benjamini-Hochberg corrections. Participants within the high group had longer illness duration than those in the low group at scale 3 (U = 40,325, p = 0.02, r = 0.16) and 4 (U = 54,104, p = 0.037, r = 0.165) in addition to a greater number of depressive episodes (scale 3, U = 52,547.5, p = 0.018, r = 0.16; scale 4, U = 69,721, p = 0.037, r = -0.15). The high group had a longer illness duration than the moderate group solely within scale 3 (U = 159,182, p = 0.037, r = -0.11). However, only the moderate group had a greater number of depressive episodes compared to the low group (U = 91,100, p = 0.037, r = -0.13) within scale 5. Lastly, the moderate group were more likely to include first-episode participants in contrast to the low group (OR = 0.78, Z = -2.913, p = 0.04). No significant differences were identified at shorter temporal scales. Depression and anxiety severity were not significantly different between any group at any temporal scale. In sum, these findings suggest that resting-state entropy can distinguish some degree of neurobiological heterogeneity within MDD, particularly at longer temporal scales for clinical trajectories rather than symptom severity. However, we highlight the strong overlap in clinical features between subgroups across temporal scales, indicating that heterogeneity in entropy is not likely to drive differences in clinical profiles within MDD.

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Poster

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Topic: H.05. Mood Disorders

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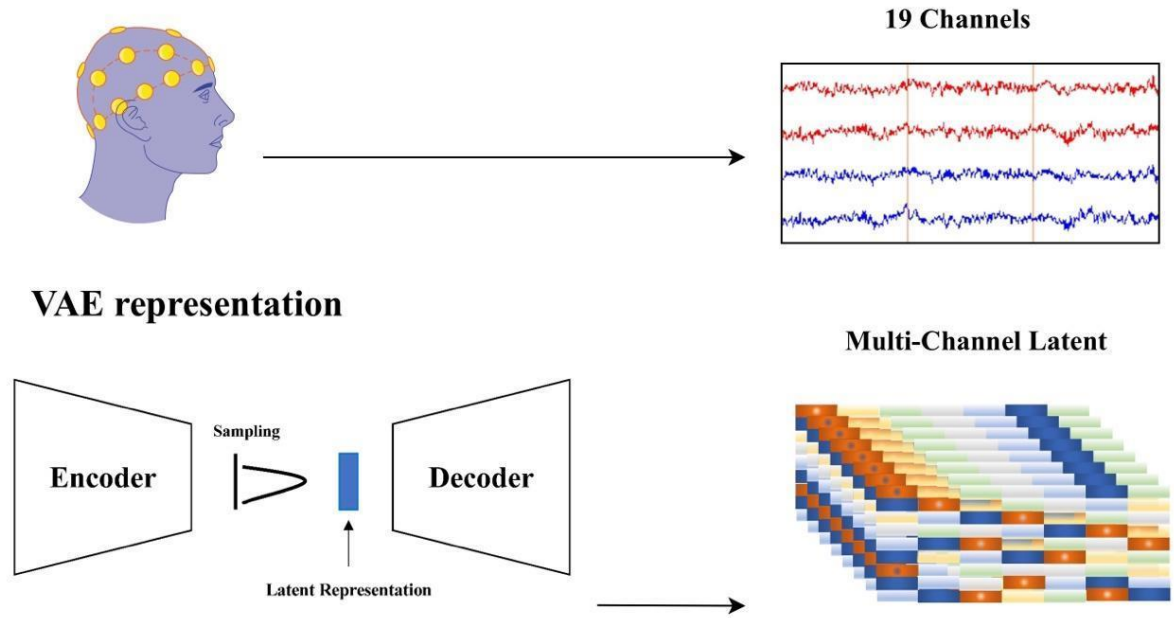
Title: Discriminating Bipolar Depression from Major Depressive Disorder Using Resting-State EEG Features Based on a GCN-LSTM Network

Authors: *&. 崔;
Gnosis Neurodynamics, Beijing, China

Abstract: Differentiating bipolar depression (BD-D) from major depressive disorder (MDD) during depressive presentations remains clinically challenging. This multicenter study internally evaluated whether resting-state EEG combined with graph-temporal deep learning could support this distinction. We included 1,290 participants recruited from three hospitals, including 732 patients with MDD and 558 with BD-D. After symptom assessment, EEG acquisition, and preprocessing, conventional EEG-feature-based machine-learning models were compared with a graph convolutional network combined with long short-term memory (GCN-LSTM). Samples were stratified by age and sex; 10% paitents were reserved as an internal test set, and the remaining data were used for eight-fold model development.

Conventional models achieved balanced accuracies of 0.645-0.655, with support vector classification performing best. The selected GCN-LSTM used weighted graph edges, a K = 4 graph-construction setting, and 15-second EEG segments. Incorporating acquisition state (eyes open/closed), sex, age, and illness duration, and using full-channel or frontal-parietal channel groups, improved validation performance. In the internal test set, the full-dataset GCN-LSTM achieved balanced accuracy of 0.731, sensitivity of 0.746, specificity of 0.716, and AUC of 0.742. The model for participants aged 45 years or younger achieved balanced accuracy of 0.732 and AUC of 0.732. Compared with the strongest conventional baseline, GCN-LSTM improved balanced accuracy by approximately 0.08. Exploratory subgroup analyses suggested stronger discrimination among participants aged 18-50 years and those with illness duration of at least 6 months.

These findings suggest that graph-based temporal modeling of resting-state EEG has preliminary value for differentiating BD-D from MDD, with moderate discrimination in an internal test set. Independent external validation, including cross-center evaluation, is required before clinical diagnostic utility can be claimed.



Disclosures: &. 崔: None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.19/II15

Topic: H.05. Mood Disorders

Title: Distinct Connectivity Profiles of the Salience and Frontoparietal Networks Govern Mind-Wandering Frequency and Affective Valence

Authors: *P. MISHRA[1], A. GUPTA[2], B. SUTAR[2], T. K. GANDHI[3];
[1]Electrical engineering, Indian Inst. of Technology, Delhi, New Delhi, India; [2]Indian Inst. of Technology, Delhi, Delhi, India; [3]Electrical Engin., Indian Inst. of Technol. Delhi, New Delhi, India

Abstract: Introduction: Mind-wandering (MW) is a complex cognitive state characterized by variations in both frequency (how often it occurs) and content (the emotional tone of the thoughts). While functional interactions among the default mode (DMN), frontoparietal (FPN), and salience (SN) networks support internal cognition, it remains unclear whether distinct neural circuits separately regulate MW frequency versus thought content. We hypothesized that dissociable resting-state circuits govern these two dimensions in young adults.**Methods**: Resting-state fMRI and behavioral questionnaire data were analyzed from healthy participants (N = 118; MPI-Leipzig Mind-Brain-Body dataset). Connectivity maps were computed among 9 regions of interest (SN, FPN, DMN, and Amygdala) to define seven circuit-level features. MW frequency was assessed using the Spontaneous and Deliberate Mind-Wandering Scale and thought quality (valence, negativity, and intrusiveness) via the Short New York Cognition Questionnaire. Ordinary least squares multiple regression and principal component analysis (PCA) were used to test brain-behavior associations. **Results:** Based on double dissociation model analysis, the quantity circuit set (internal SN, FPN-DMN) significantly predicted spontaneous ($R^2 = 0.063$, $p = 0.0237$) and deliberate ($R^2 = 0.103$, $p = 0.0020$) MW frequency, but not quality (all $p \geq 0.24$). Conversely, the Quality circuit set (SN-FPN, SN-Amygdala, SN-DMN) predicted negative thoughts ($R^2 = 0.098$, $p = 0.0083$), thought valence ($R^2 = 0.091$, $p = 0.0121$), and intrusive thoughts ($R^2 = 0.078$, $p = 0.0255$) but not frequency (all $p \geq 0.20$). Individually, deliberate MW was predicted by FPN-DMN coupling ($r = +0.318$, $p = 0.0005$), whereas thought valence and negative thoughts were predicted by SN-amygdala connectivity ($r = +0.194$, $p = 0.0353$; $r = -0.184$, $p = 0.0461$, respectively). PCA validated these dimensions: PC1 (35.9% variance) mapped to deliberate MW, PC2 (20.5%) to negative thoughts, and PC3 (13.3%) to spontaneous MW (69.8% total variance explained by PC1-3).**Conclusions:** These findings reveal that MW quantity and emotional quality are governed by orthogonal neural networks. FPN-DMN coupling controls the frequency of internal cognition, while Salience Network coupling with subcortical (amygdala) and frontoparietal systems regulates emotional valence, negativity, and thought intrusiveness. This double-dissociation model provides a mechanistic framework for understanding healthy daydreaming versus maladaptive clinical rumination.

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Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

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Title: Distinct amygdala-centered functional connections associated with diagnosis and subjective sleep quality in a double-blind, sham-controlled transcranial temporal interference stimulation study of major depressive disorder

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Abstract: Background Sleep disturbance affects most patients with major depressive disorder (MDD) and may represent a dimension partly independent of depression severity. The amygdala contributes to emotion, arousal, and sleep regulation. We tested whether amygdala functional connectivity (FC) differs by diagnosis and sleep disturbance and predicts sleep improvement following double-blind, sham-controlled right-amygdala transcranial temporal interference stimulation (tTIS). **Methods** Forty-three MDD patients (Tianjin Anding Hospital) were randomized to active (TRUE) or sham (SHAM) tTIS; baseline resting-state functional MRI (fMRI) was available in 41. Thirty controls were scanned. Amygdala FC to literature-derived regions of interest used the Brainnetome 246 atlas. The primary sleep outcome was Pittsburgh Sleep Quality Index (PSQI) total (baseline, post-treatment, 4 weeks); perceived sleep quality, sleep efficiency, and daytime disturbance were secondary. Group differences used Welch t-tests; associations and prediction used linear regression controlling for age, sex, scan session, and 17-item Hamilton Depression Rating Scale (HAMD-17) non-sleep score. Multiple comparisons used Benjamini-Hochberg false discovery rate (FDR). An independent MDD cohort (Ruijin Hospital, n=43) provided external corroboration. **Results** Versus controls, MDD showed higher right amygdala-bilateral supplementary motor area (SMA) FC (d=0.98/0.82, q=0.015/0.033) and lower right amygdala-right nucleus accumbens (NAcc) FC (d=-0.81, q=0.033). Poorer PSQI total and perceived quality were nominally linked to weaker left amygdala-medial prefrontal/cingulate FC (p=0.009-0.042); efficiency and daytime disturbance showed none. PSQI total improved post-treatment (dz=-0.50, q=0.010) and at 4 weeks (dz=-0.45, q=0.018), mainly perceived quality (dz=-0.55, q=0.005); efficiency did not change. TRUE showed no advantage over SHAM (n=25 vs 18). Baseline right amygdala-ventromedial prefrontal cortex FC nominally predicted 4-week PSQI total improvement (p=0.043) but did not survive FDR correction. In Ruijin, PSQI total similarly improved with no TRUE-over-SHAM advantage, directionally corroborating the longitudinal and null findings. **Conclusion** Right amygdala-SMA/NAcc FC differed significantly between MDD and controls, whereas left amygdala-medial prefrontal/cingulate FC showed exploratory associations with sleep. Sleep improved without TRUE-over-SHAM differences or reliable FC remodeling. Baseline amygdala connectivity related more to diagnosis and sleep heterogeneity than to short-term tTIS-induced change.

Disclosures: Y. Yang: None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.21/II17

Topic: H.05. Mood Disorders

Support: Funded by NIMH Intramural Research Program: ZIAMH002857

Title: Ketamine's antidepressant effects are linked to reward network functional connectivity

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Abstract: Background: Major Depressive Disorder (MDD) involves dysfunction within reward network circuits linked to anhedonia and motivational deficits. Ketamine, a rapid-acting antidepressant, may exert clinical efficacy by modulating reward network function. In exploratory analyses, we examined fMRI resting-state functional connectivity in MDD using a predefined reward network atlas and examined its relationship to baseline symptoms and clinical improvement following ketamine dosing.
Methods: Using a publicly available dataset (OpenNeuro ds005917), MDD participants (n = 27/session) and HC (n = 14-19/session) underwent fMRI at baseline and Day 2 post-ketamine (0.5mg/kg/40 min intravenous infusion). Functional connectivity was quantified within a reward-network atlas comprising 21 regions, including ventral tegmental area, orbitofrontal cortex, and lateral prefrontal cortex. Associations with Montgomery-Asberg Depression Rating Scale (MADRS) scores were examined cross-sectionally and longitudinally; baseline connectivity predictions of symptom change were performed using linear models adjusted for baseline severity.
Results: At baseline, higher MADRS correlated with weaker connectivity in several circuits, including mOFC-BA40 ($r = -0.46$, $p_{unc} = 0.016$) and hippocampus—BA40 ($r = -0.39$, $p_{unc} = 0.044$). There was a trend-level association between ketamine-induced change in MADRS scores with change in reward network connectivity (average of all reward network nodes; $r = -0.40$, $p = 0.067$, $n = 22$), such that greater clinical improvement was linked to decreased reward network coupling. Finally, baseline connectivity predicted Day 2 MADRS improvement for VTA-dlPFC (partial $r = 0.37$, $p_{unc} = 0.012$, $n = 24$) and dlPFC-BA37 (partial $r = 0.50$, $p_{unc} = 0.018$, $n = 24$). Edge-level analyses were exploratory and would not survive FDR correction across all reward atlas regions.
Conclusions: These findings provide preliminary evidence that MDD is characterized by baseline hypoconnectivity within cortical reward-control circuits and that individual differences in VTA-dlPFC reward connectivity may predict ketamine-related improvement more effectively than global network connectivity. Reward-network resting connectivity may serve as a useful ROI-level biomarker for treatment response. Restoring functional integration within this reward-control circuitry may promote recovery from anhedonia and motivational deficits, reflecting normalization of prefrontal-limbic signaling critical for adaptive reward processing.

Disclosures: S.O. Ogunsanmi: None. **P. Manza:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.22/II18

Topic: H.05. Mood Disorders

Support: National Institutes of Health

Title: A Pilot Randomized Trial of Multi-Target rTMS for Neuropsychiatric Symptoms of Long COVID

Authors: *B. GUZMAN[1,2], G. REMPHREY[1], R. ANVEKAR[1], J. CORLIER[1], H. AJAM OUGHLI[3], P. SIDDARTH[1], H. LAVRETSKY[1];
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Abstract: Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), commonly known as Long COVID, is associated with persistent neuropsychiatric symptoms including fatigue, sleep disturbance, pain, and depression. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive neuromodulatory intervention that modulates cortical circuit activity and has demonstrated efficacy across depression, fatigue, pain, and cognitive symptoms.This study aimed to (1) assess the safety and tolerability of rTMS and (2) evaluate the therapeutic efficacy of 30 rTMS sessions for the treatment of PASC-related neuropsychiatric symptoms (PASC-NP). 10 participants were enrolled in a 12-week randomized pilot trial (NCT06586398) and assigned to active or sham multi-target rTMS for 15 sessions, followed by 15 sessions of open-label active stimulation. Each session consisted of sequential stimulation of the left dorsolateral prefrontal cortex (DLPFC) and left primary motor cortex (M1). Clinical outcomes included depressive symptoms measured by the Patient Health Questionnaire-9 (PHQ-9); sleep, fatigue, pain, and mental health assessed using the PROMIS-29; and objective cognitive performance assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). 10 participants (active = 5, sham = 5) completed baseline and Visit 15 assessments; 9 participants completed the Visit 30 assessment (active = 4, sham = 5). At Visit 15, a significant between-group difference was observed in PHQ-9 scores ($p = 0.0025$), with the sham group showing a significant reduction in depressive symptom severity (mean change = −4.8, $p < 0.0001$) and the active group showing minimal change (mean change = +0.4, $p = 0.70$). Following the open-label active phase, the sham group demonstrated a statistically significant reduction in depressive symptom severity at Visit 30 (mean change = −6.2, p = 0.03), while the active group showed a significant reduction in sleep disturbance (mean change = −3.25, p = 0.03). Exploratory analyses revealed significant improvement in RBANS Story Memory scores from baseline to Visit 30 across all participants ($p = 0.04$). Within-group analyses further demonstrated that this effect was driven by the active group (mean change = +1.75, $p = 0.01$), whereas the sham group did not reach statistical significance (mean change = +0.60, $p = 0.50$).These preliminary findings suggest improvements in depressive symptoms, sleep disturbance, and verbal learning following multi-target rTMS in individuals with Long COVID. Larger controlled trials are warranted to further investigate the efficacy of neuromodulation for PASC-related neuropsychiatric symptoms.

Disclosures: B. Guzman: None. **G. Remphrey:** None. **J. Corlier:** None. **H. Lavretsky:** None.

Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR372.23/II19

Topic: H.05. Mood Disorders

Support: Supported by NCCIH R61AT009864 and R33AT009864 to TTY.

Title: Anterior cingulate and posterior cingulate grey matter volume changes associate with mindfulness-driven improvements in depressive symptoms in adolescents: a randomized controlled trial

Authors: *R. S. KIDAMBI[1], T. L. LUKS[2], P.-H. WU[2], T. J. HOFFMANN[3], P. YANG[4], X. LI[2], S. SINGH THAKURI[7], D. QUEZADA[8], C. Y. LEUNG[5], T. E. SAMSON[2], A. JAKARY[2], Y. LI[2], D. XU[2], J. E. MAX[9], E. EKBÄCK[10,11,12], E. HENJE[13], T. T. YANG[14,6];
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Abstract: Adolescents in the United States are increasingly experiencing depression, putting them at risk for poor academic performance, a variety of physical and mental health disorders, and suicidality. While mind-body interventions (MBIs) have shown potential in improving adolescent depression, the neural correlates underlying these changes are not yet well-understood. Prior neuroimaging studies implicate regions involved in emotional regulation, interoceptive awareness, and stress responsivity in both depression and mindfulness, with the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) standing out as particularly relevant. Training for Awareness, Resilience, and Action (TARA) is a promising, fully remotely delivered, whole-person health oriented MBI for adolescents. This study used structural MRI to investigate grey matter volume (GMV) correlates of depression improvement following TARA. Using a randomized waitlist-controlled design, 100 healthy adolescents (57 female, 43 male; mean age 15.93±1.33 years) were split into a TARA group and a waitlist control group. Each participant received a structural MRI before and after the 12-week study, with a self-report measure of depressive symptoms (Reynolds Adolescent Depression Scale-2; RADS-2). GMV was calculated for bilateral ROIs from the AAL3 atlas using voxel-based morphometry

(CAT12/SPM), including the subgenual ACC, precallosal ACC, PCC, middle frontal gyrus, insula, hippocampus, amygdala, caudate, and putamen. ANCOVAs examined the change in RADS2 as the outcome variable, and group (TARA or waitlist control) and change in each ROI GMV as between-subject factors, controlling for baseline RADS2, age, sex and total intracranial volume. Analyses were exploratory and not corrected for multiple comparisons.
89 participants completed the study (44 TARA, 45 waitlist control). We found significant interactions between group and change in right precallosal ACC GMV ($F=4.70$, $p=.033$, partial $\eta^2=.055$) and right PCC GMV ($F=6.54$, $p=.012$, partial $\eta^2=.075$). In the TARA group, decreases in both regions were associated with decreases in RADS-2, while in the waitlist control group the associations were reversed.
These findings suggest that depressive symptom change following TARA is associated with structural change in the right precallosal ACC and right PCC, warranting further study of these regions in adolescent mind and body interventions.

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Poster

PSTR372: Mood Disorders: Human Imaging and Behavioral Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.24/II20

Topic: H.05. Mood Disorders

Support: NIH F31 MH136784.

Title: Epigenetic differences in post-mortem brain samples correspond with impulsive behavior in mood disorders

Authors: *J. PERSON[1], E. J. VALLENDER[2], H. PANTAZOPOULOS[3], C. A. STOCKMEIER[1];
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Abstract: Rationale: Impulsive behavior often occurs in people with mood disorders and is associated with worse health outcomes and an increased likelihood of death by suicide. Studies have linked several genes with impulsive behavior through GWAS, but there is relatively little information on the genetic underpinnings of impulsive behavior linked to mood disorders and potential brain regions in which differential gene expression related to impulsivity within mood disorders occurs. Objectives: The current study sought to correlate degree of impulsivity and differential expression of genes in key brain regions in a cohort of posthumous subjects diagnosed with mood disorders. Methods: Adult post-mortem brain tissue from the dorsolateral

prefrontal cortex (dlPFC) and orbitofrontal cortex (OFC) of adult humans was sorted into three groups: control, mood disorder with impulsivity, and mood disorder without impulsivity. All subjects were scored on a measure of impulsivity using select questions from the Structured Interview for DSM-IV Personality Disorders (SIDP), which was completed by next-of-kin. Bulk tissue RNA sequencing was performed on both brain areas, and gene expression was correlated with impulsivity scores. Results: Bioinformatic analysis of RNA sequencing data revealed differential gene expression among individuals with mood disorder corresponding with increasing impulsivity scores. Thirty-eight genes were found to be differentially expressed in the OFC, and 5 genes in the dlPFC in the mood-disorder cohort. Conclusion: The genes identified to be correlated with impulsive behavior provide mechanistic information regarding the manifestation of mood disorders and co-occurring impulsive behavior. The measured differential expression of these genes provides insight into the transcriptional changes underlying these behaviors. Identifying the placement and function of the associated proteins may facilitate the development of therapeutics to mitigate the damages associated with these co-occurring behavioral phenotypes.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.01/II21

Topic: H.05. Mood Disorders

Support: NIDA P50 DA044118
NIMH T32MH119049

Title: Adolescent THC exposure produces persistent and sex-dependent alterations in risk-based decision making

Authors: *S. DIRIK[1], M. X. MARTINEZ[2], C. M. RUIZ[2], S. V. MAHLER[2];
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Abstract: Neuroplasticity during adolescence is a double-edged sword - the same developmental processes that enable rapid acquisition of skills and adaption to an ever-changing environment also result in impulsivity and risk taking that can lead to negative consequences. Furthermore, many psychiatric disorders onset during adolescence, and initiation of drug use may exacerbate this emergence by altering neurodevelopment itself, with potentially life-long consequences. Cannabis is one of the most popular substances used by teenagers, and exposure to its active ingredient THC early in adolescence is linked to disorders including schizophrenia, anxiety and depression. Though the direction of causation is debated in humans, preclinical studies suggest that early cannabis use induces changes in cognition, emotional regulation, and motivation that

persist into adulthood. Such changes could extend to altered reward and threat processing, and top-down regulation thereof, that contribute to broader maladaptive decision making patterns characteristic of several psychiatric disorders.
Here we aim here to further characterize the specific behavioral processes impacted by AdoTHC in rats, and to identify the neural changes underlying them. To address this question, male and female rats were subjected to our well-characterized adolescent THC exposure regimen (AdoTHC) during early-to-mid adolescence (PD30-43), followed by a 21-day washout period. In adulthood, rats were then evaluated in an operant risky decision making task where decisions about reward pursuit are made in the presence of variable threat of footshock. The same rats were also tested for sensitivity to reward or threat in the absence of the competing motivational pressure. We further investigated the neural correlates of these behaviors in AdoTHC and control rats with regional c-Fos analyses.
AdoTHC produced persistent, sex-dependent alterations in reward, threat, and risky decision making, which were accompanied by changes in neural activity. These findings suggest that AdoTHC produces enduring changes in the motivational processes that guide decision making, and point to the specific psychological and neural processes that may be involved in the link between early cannabis use and psychiatric vulnerability later in life.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.02/II22

Topic: H.05. Mood Disorders

Support: R01MH106500
1F99NS135696-01

Title: Neuronal, Microglial, and Molecular Adaptations of the Nucleus Accumbens in Chronic Social Stress

Authors: *D. FRANCO[1], B. M. SIEMSEN[2], G. KUMAR[1], S. KEY[1], P. DAS[1], J. OLUSAKIN[1], M. E. FOX[3], M. LOBO[4];
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Abstract: Chronic stress is a significant risk factor for neuropsychiatric disease, such as major depressive disorder. To investigate the neurobiological mechanisms through which stress gives rise to depressive-like phenotypes, preclinical paradigms such as chronic social defeat stress (CSDS) and chronic witness defeat stress (CWDS) are employed to model direct and indirect social stress, respectively. Prior work examining stress-induced outcomes in the nucleus

accumbens, a key brain region associated with reward and motivation, characterized dopamine receptor D1 -expressing medium spiny neuron (D1-MSN) dendritic atrophy in mice after CSDS. However, the cellular mechanisms underlying this morphological vulnerability remain unclear. Here, we investigate whether microglia, the brain's resident immune cells, contribute to stress-induced D1-MSN atrophy, and how this neuron-microglia relationship differs across CSDS male and CWDS male and female mice. Using confocal microscopy, microglial and D1-MSN morphological reconstruction, quantification of MSN-microglia contact, pharmacological microglial depletion (PLX5622), and temporal transcriptional profiling, we characterized the cellular, molecular, and behavioral landscape of the NAc across three cohorts. D1-MSN dendritic atrophy emerged as a convergent consequence of all three stress paradigms, yet the accompanying microglial morphological profiles, microglia-D1-MSN contact patterns, and transcriptional trajectories diverged markedly across sex and paradigm. Microglial depletion partially rescued D1-MSN atrophy in both sexes, with a sex-dependent dose-response revealing distinct microglial roles in males and females. Temporal transcriptional profiling identified three distinct kinetic response profiles and revealed that microglial state transitions unfold dynamically across the stress course, including a biphasic morphological trajectory in males. Together, these findings establish that microglia contribute to stress-induced D1-MSN structural pathology through sex- and paradigm-specific cellular and molecular routes that converge on shared structural and behavioral endpoints. This work reframes microglia-neuron interactions in chronic stress as dynamic, temporally extended processes rather than static states, and underscores the necessity of multi-modal, sex-stratified approaches for understanding, and ultimately treating, stress-related neuropsychiatric and substance use disorders.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

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Program #/Poster #: PSTR373.03/II23

Topic: H.05. Mood Disorders

Support: R01MH106500

Title: Chronic social stress transiently suppresses striatal mitochondrial complex I and IV activity

Authors: *P. DAS[1], C. A. CALARCO[2], M. ROWELL[3], S. N. SCOTT[5], D. FREEMAN[4], S. GANAPATHY-KANNIAPPAN[1], B. M. POLSTER[6], M. LOBO[7];
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Abstract: Chronic stress is one of the most predominant risk factors for Major Depressive Disorder (MDD), and converging evidence suggests impaired brain energy metabolism in its pathophysiology. Mitochondrial function in the ventral striatum (nucleus accumbens- NAc) shapes motivation, social hierarchy (dominant vs subordinate), and stress susceptibility. Yet, how chronic social stress alters mitochondrial electron transport chain (ETC) activity across striatal regions in social stress paradigms is unclear. We examined the both NAc and dorsal striatum (DS) in male C57BL/6J mice exposed to chronic social defeat stress (CSDS) and female mice exposed to chronic witness defeat stress (CWDS), as well as stress-naïve controls. Striatal regions were collected after 2 hours or 48 hours after the last stress-exposure. The activity of complex I, complex II, and complex IV were measured using CRABS-ROC assay. At 2-hour, stress reduced complex I and complex IV activity in both DS and NAc, in CSDS males and CWDS females. By 48 h, ETC activity in stressed mice did not differ from controls in NAc, indicating a transient, recoverable bioenergetic deficit rather than a sustained one. Additionally, preliminary data mimicking stress induced molecular regulation of dendritic atrophy in NAc dopamine receptor 1 expressing medium spiny neurons with adeno-associated virus (AAV) RhoA overexpression in NAc D1-MSNs reduced individual mitochondrial size relative to control AAV, consistent with RhoA-driven, Drp1-dependent fission. Together, these data show that chronic social stress produces an early suppression of complex I and IV activity in NAc and DS of both sexes. Further, this study implicates RhoA as a candidate regulator of stress-related mitochondrial remodeling in the NAc. RhoA-mitochondrial coupling may link cytoskeletal and bioenergetic responses to stress, offering a potential therapeutic target for stress-related mood disorders.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

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Program #/Poster #: PSTR373.04/II24

Topic: H.05. Mood Disorders

Support: University of Connecticut Research Foundation
UCONN IBACS

Title: Effort-related motivational effects of the atypical dopamine transport inhibitor vanoxerine in rodent models of decision-making: Interactions with the SSRI fluoxetine and the norepinephrine transport inhibitor atomoxetine.

Authors: *J. D. SALAMONE[1], G. A. EDELSTEIN[2], J. N. MILLER[2], K. R. FLORA[2], S. PAPANIKOLAOU[2], M. NARAYANAN[2], P. MATAS NAVARRO[3], M. CORREA[3]; [1]Psychological Sci., [2]Psychological Sciences, Behavioral Neurosci., Univ. of Connecticut, Storrs, CT; [3]Psicobiologia, Univ. Jaume I, Castello, Spain

Abstract: Motivational symptoms (e.g. fatigue, anergia, apathy, avolition) are seen in several disorders, including depression, schizophrenia, and Parkinsonism. These symptoms are highly debilitating, and commonly prescribed antidepressants (e.g. serotonin selective transport (SERT) inhibitors) are relatively ineffective at treating them. Dopamine (DA) plays a key role in several aspects of motivation, including behavioral activation and exertion of effort. Human and rodent research shows that inhibiting the DA transporter (DAT) modulates selection of high-effort activities. In studies of effort-based choice, animals are given the option of exerting high levels of effort (e.g., lever pressing) to obtain a preferred reinforcer (high carbohydrate food pellets) vs. a low effort/less preferred option (e.g., approaching and consuming chow). The vesicular monoamine transport (VMAT-2) inhibitor tetrabenazine (TBZ) induces depressive symptoms, fatigue, and apathy in people, and produces a low-effort bias in rodents tested on effort-based choice. Drugs that inhibit DAT, such as bupropion, reverse the effects of TBZ, while drugs that selectively inhibit 5-HT or norepinephrine transport (NET) are ineffective. Classical DAT inhibitors such as cocaine have high abuse liability, but there is considerable variability in how DAT ligands interact with the transporter; not all DAT ligands are major stimulants. Ongoing studies show that atypical DAT inhibitors such as vanoxerine (GBR 12909), as well as modafinil and several of its analogs, are effective at reversing the effort-related actions of TBZ and enhancing selection of high-effort activities. Vanoxerine produces a robust reversal of the effort-related effects of TBZ in both male and female rats. In contrast, the triple uptake inhibitor diclofensine produces only a modest reversal of the effects of TBZ in male rats, with no effect in females. To investigate the possibility that blockade of SERT or NET act to blunt the effects of DAT inhibition, we studied the combined effects of DAT inhibition and blockade of SERT with the SSRI fluoxetine and NET with the selective inhibitor atomoxetine. Injection of the SERT inhibitor fluoxetine (Prozac) with vanoxerine did not enhance the ability of the DAT inhibitor to reverse the effects of TBZ. Rather, fluoxetine suppressed lever pressing when given in combination with vanoxerine. Similar results were obtained with atomoxetine. These results emphasize the significant role that DA transmission has in regulating exertion of physical effort and effort-based decision making, which has implications for treating effort-related motivational dysfunctions in psychopathology.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

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Program #/Poster #: PSTR373.05/II25

Topic: H.05. Mood Disorders

Support: Institute for the Brain and Cognitive Sciences (IBACS)
University of Connecticut Research Foundation

Title: Mouse touchscreen models of effort-based choice for assessing motivational dysfunction: Evaluation of the atypical DAT inhibitor Vanoxerine

Authors: *J. N. MILLER[1], G. A. EDELSTEIN[2], A. O'BOYLE[3], M. CORREA[5], J. D. SALAMONE[4];
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Abstract: Motivational dysfunction is prevalent symptom subset seen across a number of psychopathologies, characterized fatigue, anergia, apathy, avolition, and reduced effort expenditure. These debilitating symptoms are highly treatment resistant, and selective serotonin transport inhibitors are relatively ineffective at treating motivational dysfunction, highlighting the need for novel therapeutic development. Evidence indicates that manipulating dopamine (DA) transmission by antagonizing DA receptors or inhibiting the DA transporter (DAT) - with high selective compounds such as vanoxerine (GBR12909) or less selective, dual reuptake inhibitors like Wellbutrin (bupropion) - can modulate the exertion of effort in humans and rodent models of effort-based decision-making. Current studies demonstrate that there are sex differences in treatment response, signifying the need to assess compounds in both male and female subjects when determining therapeutic efficacy. In the current study, mice were trained on a fixed ratio schedule in which a panel press corresponds with the dispensing of the preferred reinforcement, strawberry Ensure. Mice are then introduced to the progressive ratio (PROG) pellet task; a more difficult task as the response requirement increases throughout the session. High carbohydrate pellets are then introduced into the chamber, allowing the mice a choice between exerting effort for the more preferred reinforcement or consuming the low effort alternative, freely available pellets. If mice fail to complete a ratio within a specified period of time, the availability of the panel pressing disappears. At baseline, male and female C57BL/6 mice show relatively low panel pressing and pellet intake above one gram. Various compounds are then assessed for their ability to enhance the selection of the high effort behavior (panel pressing), assessing for the therapeutic potential of various compounds as for treating the low effort bias associated with motivational dysfunction symptoms seen in depression and other disorders. Results indicate that the DAT inhibitor vanoxerine shifted choice, enhancing the selection of the high effort panel pressing, while the serotonin selective transport inhibitor fluoxetine (Prozac) did not. These findings highlight the role of DA in regulating selection of high-effort activities, and emphasize the potential utility of mouse touchscreen procedures.

Disclosures: J.N. Miller: None. **G.A. Edelstein:** None. **A. O'Boyle:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

PSTR373: Mood Disorder and Reward-Related Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.06/II26

Topic: H.05. Mood Disorders

Support: Institute for the Brain and Cognitive Sciences
University of Connecticut Research Foundation
The Center for Advancement of Managing Pain

Title: Evaluation of Antidepressants for Attenuation of Effort-Related Motivational Dysfunction in Male and Female Rats: The Importance of Dopamine Transport Inhibition

Authors: *G. EDELSTEIN[1], J. MILLER[1], A. ECEVITOGLU[4], A. BESIREVIC[1], G. ROMAN[5], N. CYR[1], A. O'BOYLE[1], K. FLORA[1], A. GOLDHAMER[2], M. CORREA[6], J. D. SALAMONE[3];
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Abstract: In addition to mood dysfunctions, major depressive disorder (MDD) is characterized by debilitating motivational symptoms such as anergia, fatigue and apathy, which are resistant to commonly prescribed antidepressants. Monoamine transport (MAT) inhibitors are the most common treatments for depression, but across drugs there are many different profiles of action on distinct MAT proteins. Drugs such as serotonin (5-HT) transport (SERT) inhibitors are relatively ineffective at treating motivational impairments and can even exacerbate them, while drugs inhibiting dopamine (DA) and norepinephrine (NE) transporters (DAT and NET) such as bupropion are relatively effective at treating motivational symptoms. Sex differences in MDD prevalence and symptom presentation have been reported, but research assessing sex differences in response to antidepressant treatment is lacking. Rodent tests of effort-based choice are used as models for assessing the pro-motivational effects of drugs. The present studies assessed the ability of various DAT, NET and SERT inhibitors to reverse the low-effort bias induced by the vesicular monoamine transport type 2 inhibitor tetrabenazine (TBZ) in male and female rats. TBZ produces depressive side effects, including fatigue and apathy, in humans. In rats tested on the fixed ratio 5/ choice task, TBZ shifts behavior, reducing lever pressing but increasing chow intake. Drugs that inhibit DAT, including the selective atypical DAT inhibitor vanoxerine (GBR12909), reverse the behavioral effects of TBZ in male and female rats but drugs that selectively inhibit NET or SERT fail to do so. Drugs that inhibit DAT produce different dose-related behavioral effects across sexes, and females show larger increases in extracellular DA following administration of some DAT inhibitors, as measured by microdialysis. In summary, facilitation of DA transmission is critical for the attenuation of effort-based motivational dysfunctions, but sex differences must also be taken into account.

Disclosures: G. Edelstein: None. **J. Miller:** None. **A. Ecevitoglu:** None. **A. Besirevic:** None. **G. Roman:** None. **N. Cyr:** None. **A. O'Boyle:** None. **K. Flora:** None. **A. Goldhamer:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

PSTR373: Mood Disorder and Reward-Related Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.07/II27

Topic: H.05. Mood Disorders

Title: Long-term chemogenetic activation of ventral hippocampal projections to the nucleus accumbens alters social novelty and locomotor organization in rats

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Abstract: Schizophrenia is increasingly conceptualized as a disorder of distributed circuit dysfunction, with converging evidence implicating hippocampal hyperactivity as an upstream driver of mesolimbic dysregulation. In particular, elevated ventral hippocampal (vHPC) output has been proposed to contribute to aberrant salience processing and psychosis-relevant behavioral states. However, it remains unclear whether chronic, projection-specific hyperactivity of the vHPC → nucleus accumbens (NAc) pathway is sufficient to induce a coherent behavioral phenotype relevant to schizophrenia-associated dysfunction. Here, we used a dual virus chemogenetic strategy to chronically excite vHPC neurons projecting to the NAc in male LE rats. Animals received a retrograde Cre-expressing virus in the NAc and a Cre-dependent hM3Dq construct in the vHPC, followed by behavioral testing under chronic clozapine-N-oxide (CNO) exposure for >14 days. We assessed social preference, social novelty, conflict-related exploration in the modified elevated T-maze (mETM), and amphetamine-induced locomotor responses. To resolve features of behavior not captured by conventional locomotor measures, we additionally quantified spatial entropy and Katz fractal dimension (FD). Chemogenetic activation of ventral hippocampal projections to the NAc did not abolish sociability, as both groups showed preference for a social stimulus over an object. However, hM3Dq rats showed impaired social novelty discrimination under CNO, whereas control rats showed the expected preference for novelty. Similarly, the modulation didn't produce a broad anxiety-like phenotype rather than affected the risk assessment and conflict-sensitive aspects of the behavior. Amphetamine treatment increased locomotor distance in an open field in a dose-dependent manner irrespective of chemogenetic activation of the vHPC → NAc projection. Subsequent in-depth analyses using FD and entropy-based measures revealed group-dependent changes in the structure and organization of movement patterns that were not fully captured by distance alone. These findings suggest that activation of ventral hippocampal projections to the NAc selectively disrupts social novelty recognition while preserving basic sociability, affects ethological indices of risk assessment behavior and alters the organization of psychostimulant-induced behavior. Projection-specific ventral hippocampal output to the NAc may therefore contribute to schizophrenia-relevant abnormalities in behavioral salience and regulation in rats.

Disclosures: Z. Balla: A. Employment/Salary (full or part-time):; employed by Boehringer Ingelheim Pharma. **J.V. Schweimer:** A. Employment/Salary (full or part-time):; employed by

Boehringer Ingelheim Pharma. **C.T. Wotjak:** A. Employment/Salary (full or part-time):; employed by Boehringer Ingelheim Pharma.

Poster

PSTR373: Mood Disorder and Reward-Related Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.08/II28

Topic: H.05. Mood Disorders

Support: ZIAMH002881 to ZL

Title: A Mouse Model of Frustrative Non-Reward Reveals Brain Network Reorganization Associated with Frustration-Related Behaviors

Authors: *A. A. NAIK, Z. LI;
NIH/NIMH, Bethesda, MD

Abstract: Irritability, a symptom shared across multiple psychiatric disorders including disruptive mood dysregulation disorder (DMDD), arises from maladaptive responses to frustrative non-reward (FNR), a construct with the Negative Valence Systems domain of the Research Domain Criteria (RDoC) framework. To investigate the neural basis of FNR, we developed APRO (Alternate Poking Reward Omission), a new behavioral task for mice. In sex-balanced cohorts, FNR exposure increased aggression and locomotor activity while leaving anxiety-like behavior, depression-like behavior, and non-aggressive social interactions unchanged. The APRO task reproduces key features of FNR response, particularly increased motor activity and aggression. Whole-brain cFos mapping and TRAP2-mediated activity-dependent tagging revealed significant neuronal activation in cortical and subcortical regions, indicating recruitment of a distributed neural network. Brain-wide network analysis of c-Fos activity showed that FNR reshapes network organization by reorganizing modular architecture and shifting information processing toward greater global integration, reflected by increased intermodular connectivity and reduced segregation. This pattern resembles connectivity changes reported in irritable youth, supporting the translational relevance of our FNR model. Together, the behavioral and neural changes induced by APRO suggest that FNR engages coordinated neuronal ensembles across interconnected brain regions to drive frustration-related responses in mice during repeated reward omission challenges. These findings establish a robust preclinical platform for probing FNR mechanisms and identifying therapeutic targets for irritability.

Disclosures: A.A. Naik: None. **Z. Li:** None.

Poster

PSTR373: Mood Disorder and Reward-Related Behavior

Location: WCC Halls A-C

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Topic: H.05. Mood Disorders

Support: NIH Grant 1R01DA055849-02
NASEM Ford Foundation Fellowship to EMR
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Title: Stay Home or Go Out? How Ventral Pallidal GABA Neurons Influence Social Motivation Alone and in the Context of Drug Use

Authors: *E. RAMIREZ[1], S. WALAWALKAR[1], H. VU[1], S. LOPEZ-ORRACA[3], R. ROKERYA[1], C. SUMARINAS[1], E. ARELLANO[1], S. V. MAHLER[2];
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Abstract: Social connection is a fundamental component of mental health and well-being, yet we still have a limited understanding of the neurobiology underlying the desire to be together. Many psychiatric disorders including addiction are strongly influenced by social factors that are often overlooked. It is thus important to uncover the circuits involved in social motivation in order to better understand how these processes are disrupted in disease. Here we report a series of studies examining how GABA neurons in the ventral pallidum (VP), a brain region well known to mediate aspects of food and drug reward seeking, are involved in social behaviors, as well as social modulation of drug reward. In transgenic GAD1-Cre Long Evans male and female rats, we chemogenetically inhibited or stimulated VP GABA neurons during social- and drug-related behaviors, testing effects on social interactions themselves, as well as on motivated seeking of social-reward, intravenous heroin-reward, and also choice of social interaction or drug, but not both. To do so, wildtype and excitatory or inhibitory VP GABA DREADD-expressing rats were socially isolated prior to undergoing assessments of 1) conditioned place preference for their separated cagemate, 2) social play and investigation of the cagemate, 3) social communication via ultrasonic vocalizations, 4) operant self-administration of cagemate interaction time, and 5) operant, mutually-exclusive choice of social versus heroin reward opportunities. We also used calcium imaging of VP GABA neurons to assess the timing of their spontaneous activity during some of these behaviors. Our findings demonstrate a clear domain- and sex-specific role for VP GABA neurons in social reward seeking, social investigation, and social communication behaviors in rats, and explore VP participation in the delicate balance of social and drug reward that is likely to play an underappreciated role in addiction. These results highlight the underappreciated role of the VP in social reward, motivation, and communication as well as opioid drug seeking, and suggest potential future intervention strategies for helping treat addiction by shifting drug seeking motivation into healthier directions. They also advance understanding how social factors modulate opioid drug seeking in addiction more generally. It is our hope that by untangling the neural circuit substrates involving VP that impact social and drug rewards, we may develop new approaches for leveraging social factors in preventing or treating addiction.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

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Program #/Poster #: PSTR373.11/II30

Topic: H.05. Mood Disorders

Support: NIDA grant R01 DA055849

Title: Evaluating Acute Psilocybin Treatment in Reversing Trauma-Induced Phenotypes in Rats

Authors: *B. MORALES[1], P. RANTA[2], S. V. MAHLER[3];
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Abstract: Psychedelic drugs have re-emerged as a potential treatment for psychiatric disorders, including post-traumatic stress disorder (PTSD). Our group previously showed that administering a single dose of the serotonergic psychedelic DOI in a comfortable setting reduces hyperreactivity to a mild stressor in previously "traumatized" rats—a behavioral phenomenon called stress-enhanced fear learning (SEFL). Here we sought to replicate and extend this finding with the more clinically-relevant psychedelic drug psilocybin. We aimed to characterize the conditions and doses in which psilocybin reduces trauma-like phenotypes, and additionally, uncover potential sex differences and neural substrates that drive this effect. These studies will thereby advance our understanding of the behavioral and biological mechanisms underlying "psychedelic therapy." Female and male Long Evans rats were first subjected to unpredictable, inescapable shocks in a specific context (Context A). No-shock control rats were placed into Context A for the same duration without shock. Rats were extinguished of this contextual "trauma" association over the next 4 days by placing them in Context A without further shocks. Rats were also habituated to a separate tub cage (the "Treatment Context") on the same days, following each extinction session. The following day (5 days after "trauma"), they were given psilocybin (low or high dose) or saline and placed in the "Treatment Context" for an hour. Effects of psilocybin on head twitch responses and ultrasonic vocalizations were quantified in this hour. Rats were then returned to home cage for 2 days. Lastly, rats underwent a SEFL test, in which they were placed into a novel Context B, and then administered a single foot shock. Freezing during this session was analyzed as an index of shock-elicited fear. As expected, "traumatized" rats froze more than no-shock control rats following the single Context B shock. We found that psilocybin alters behavior both acutely (in the hour following drug administration) and persistently (freezing during the SEFL test) in a sex- and dose-dependent manner. We also report effects of trauma and/or psilocybin on brain activity using regional c-Fos expression analyses. This study adds to a growing body of evidence suggesting that psychedelic therapy can be successfully modeled in rats, and demonstrates a behavioral procedure well-suited for doing

so. Results may point toward novel biological mechanisms that can help advance and refine the use of psychedelic drugs in clinical settings for treatment of disorders like PTSD.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR373.12/II31

Topic: H.05. Mood Disorders

Support: DAIP, CIIC 2026, Universidad de Guanajuato.

Title: Murine model of ADHD and evaluation of natural products

Authors: *C. ALBA-BETANCOURT[1], K. ORTEGA SANCHEZ[1], O. JARAMILLO-MORALES[2], A. ALONSO-CASTRO[3], D. GASCA-MARTINEZ[4], M. DEVEZE ALVAREZ[1]; [1]Univ. De Guanajuato, Guanajuato, Mexico; [2]Dept. de Enfermería y Obstetricia, Univ. de Guanajuato, Ciudad de México, Mexico; [3]Univ. of Guanajuato, Guanajuato, Mexico; [4]Behavioral Analysis Unit, Neurobio. Institute, UNAM Campus Juriquilla, Queretaro, Mexico

Abstract: The establishment of experimental models of attention-deficit/hyperactivity disorder (ADHD) represents a crucial step toward understanding the core features of this condition and exploring potential therapeutic strategies. Current pharmacological treatments for ADHD are associated with adverse effects and are classified as substances with abuse potential. In this project, we aimed to develop an ADHD model using lead acetate, with the objective of creating a simple and accessible system that complies with PETA specifications. Male B57BL/6 mice, three weeks of age (13 g), were exposed for four weeks to lead acetate at a concentration of 180 mg/L administered through drinking water. Following exposure, the animals were subjected to behavioral assessments designed to evaluate hallmark features of ADHD, including impulsivity, measured by cliff avoidance tests, and hyperactivity, assessed using the open-field paradigm. Control animals receiving vehicle did not exhibit these behaviors, whereas lead acetate-treated mice demonstrated a significant increase in both hyperactivity and impulsivity. Subsequently, the animals were treated with verbenone, a monoterpene with reported anti-inflammatory and antioxidant properties, at doses of 10, 50, and 100 mg/kg body weight. A dose-dependent reduction in impulsivity and hyperactivity was observed, supporting the potential of verbenone as a modulatory agent in this experimental ADHD model.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

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Program #/Poster #: PSTR373.13/II32

Topic: H.05. Mood Disorders

Support: NIH Grant AT013189
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NIH Grant ES036997

Title: Multidimensional sociability trajectories predict neural connectivity following chronic social stress

Authors: *S. NIETUBICZ[1], C. LU[2], J. BENSON[4,3], S. KIM[5], Z. KUANG[6], D. MELING[4], J. GOENSE[4], H. GRITTON[7], D. ZHAO[4], P. J. BONTHUIS[3];
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Abstract: Chronic social defeat stress (CSDS) is a widely used mouse model of stress-induced depression-like behavior, in which mice are typically classified as resilient or susceptible based on a strict cutoff for a single social interaction metric following defeat stress called the social interaction ratio (SI). However, this binary definition overlooks pre-stress baseline behavioral differences, reduces resilience to a single dimension, and obscures continuous variation in the degree and nature of social interaction. To address these limitations, we explored a multidimensional measure of the effects of social defeat stress by applying principal components analysis to a panel of pre- and post-CSD behavioral measures in mice that underwent CSD. Our first component captured a generalized avoidance tendency, characterized by increased time in corner zones located far from a social stimulus and reduced time in the social interaction zone near a stimulus, both before and after CSD. Our second component reflected stress-induced behavioral change, captured as the difference in sociability before versus after CSD. Both dimensions more effectively distinguished CSD-exposed mice from controls than the conventional post-CSD SI ratio. We then examined associations between these dimensions and resting-state fMRI connectivity following CSD. Whereas the standard post-CSD SI ratio measure showed no significant relationship to connectivity among brain regions implicated in social defeat stress, both PCA-derived dimensions were associated with multiple region-pair connectivity relationships (FDR < 0.10). To determine whether multidimensionality alone accounted for these findings, we repeated our analyses using post-CSD behaviors only. The resulting components showed no significant associations with brain connectivity, indicating that incorporating pre-CSD behavioral measures is critical for capturing biologically meaningful variation in stress resilience. These findings suggest that resilience is best conceptualized as a continuous, multidimensional process shaped by individual behavioral trajectories rather than a static post-CSD outcome. By quantifying latent dimensions of stress trajectories, this new

framework may improve identification of neural circuits underlying vulnerability and resilience to stress-related mental illness.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

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Program #/Poster #: PSTR373.14/JJ1

Topic: H.05. Mood Disorders

Support: 2024 NARSAD Young Investigator Grant 32684

Title: Ketamine Reverses Anhedonia-Like Behavior in an AKAP11 Knockout Mouse Model of Schizophrenia-Bipolar Disorder Risk

Authors: *J. CHOI[1], S. AYGAR[1], A. R. LARK[1], N. AMBAREEN[1], F. A. MIR[1], C. J. NEHS[1,2]; [1]Dept. of Anesthesiol., Mass Gen. Brigham, Boston, MA; [2]Div. of Sleep Med., Harvard Med. Sch., Boston, MA

Abstract: Ketamine's antidepressant effects have been explored in wild-type rodents with stress-induced depressive-like behavior; however, its efficacy in genetic models relevant to psychiatric disease risk remains unclear. *AKAP11* (A-kinase anchoring protein 11) has been identified as a rare variant gene shared between schizophrenia and bipolar disorder.
We examined the behavioral and molecular effects of ketamine in *AKAP11* homozygous knockout (KO) mice and wild-type (WT) littermates. Mice received saline (SAL) or ketamine (KET; 5 mg/kg, i.p., daily for 21 days). Behavioral assays included the sucrose preference test (SPT), open field test (OFT), and forced swim test (FST). Hippocampal brain-derived neurotrophic factor (BDNF) and superoxide dismutase 2 (SOD2) levels were quantified using ELISA. Data were analyzed using two-way ANOVA (genotype × treatment) with post hoc comparisons.
A significant genotype × treatment interaction was observed in SPT ($p < 0.0001$). KO-SAL mice exhibited reduced sucrose preference compared to WT-SAL (mean difference, −18.11%; 95% CI, −29.9 to −6.2; $n = 14$/group), indicating anhedonia-like behavior. Ketamine normalized sucrose preference in KO mice (KO-KET vs. WT-SAL: mean difference, 0.28%; 95% CI, −13.1 to 13.7; $n = 9, 14$). Sucrose preference was positively correlated with hippocampal BDNF levels ($R^2 = 0.103$, $p = 0.023$). KO mice also showed reduced locomotion in OFT relative to WT (main effect of genotype, $p < 0.0001$), which was not altered by ketamine. Hippocampal SOD2 levels were positively correlated with the number of center entries in the OFT ($R^2 = 0.347$, $p = 0.006$). No significant effects were observed in FST.
These findings indicate that ketamine selectively reverses anhedonia-like behavior in *AKAP11* KO mice, with sucrose preference positively associated with hippocampal BDNF levels. This

model may be useful for studying ketamine-responsive behavioral phenotypes relevant to schizophrenia-bipolar disorder genetic risk.

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Poster

PSTR373: Mood Disorder and Reward-Related Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.9/JJ2

Topic: H.05. Mood Disorders

Title: Nondopaminergic mechanisms during acute withdrawal following methamphetamine treatment

Authors: *I. M. WHITE[1], W. WHITE[2];
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Abstract: Previously, we reported that amphetamine (2 mg/kg) increased activity for several hours after treatment, followed by decreased activity, a sign of acute withdrawal,13-24 hours after treatment. SCH 23390 (0.05 mg/kg), D1 antagonist, blocked both acute and withdrawal effects. This study examined non-dopaminergic contribution to acute withdrawal using methamphetamine (METH), which is a similar psychostimulant with a greater serotonin transmission compared to amphetamine. Male and female Wistar rats were given saline, METH (1 mg/kg, 1.5 mg/kg), and SCH 23390 (0.05 mg/kg). All injections were done near the light-onset of a 12/12-hour light/dark cycle. Activity was measured in open fields for 24 hours following treatments. In both males and females, METH produced large increases in activity during the first several hours following treatment, with less forward locomotion and more stereotypy following the high dose. 1 mg/kg METH produced differential effects 13-24 hours after treatment: a sign of acute withdrawal in females but not in males. D1 antagonist reliably blocked both the shorter-term and acute withdrawal effect. When METH dose increased to 1.5 mg/kg, acute withdrawal appeared more likely but less affected by D1 antagonist. Given our previous report that a moderate dose of escitalopram blocked amphetamine-induced acute withdrawal, our findings suggest that changes in a non-dopaminergic system, particularly lack of serotonin, may affect the acute withdrawal state, and that the depression-like state during psychostimulant withdrawal may reflect an altered state of a serotonin system.

Disclosures: I.M. White: None. **W. White:** None.

Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR374.01/JJ3

Topic: H.05. Mood Disorders

Support: GRF CityUHK 11101521
GRF CityUHK 11103922
GRF CityUHK 11104923
GRF CityUHK 11104524

Title: Basolateral amygdala drives depression by reshaping prelimbic inhibitory networks

Authors: *H. WANG[1], M. ASIM[2], J. HE[1];
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Abstract: Aberrant interactions between the basolateral amygdala (BLA) and the medial prefrontal cortex(mPFC) are a hallmark of major depressive disorder. However, the circuit-level mechanisms by which amygdala hyperactivity perturbs prefrontal processing remain poorly understood. Here, we demonstrate that excitatory projections from the BLA to the prelimbic cortex (PrL) drive depressive-like states by recruiting local inhibitory networks to suppress prefrontal excitatory output. Optogenetic activation of BLA-PrL terminals induces robust behavioral despair anhedonia, which can be mitigated by chemogenetic inhibition of PrL GABAergic neurons. Furthermore, chronic activation of BLA excitatory neurons replicates core features of depression and drives a profound excitatory-inhibitory (E/I) imbalance in the PrL. Dissecting this inhibitory network, we found dynamic involvement of parvalbumin (PV)- and somatostatin (SST)-expressing subpopulations, yet identified cholecystokinin (CCK) interneurons as the critical hub. Crucially, the BLA-driven local release of the neuropeptide CCK is essential for orchestrating this depressive phenotype, and targeted inhibition of CCK signalling or these specific cells is sufficient to attenuate the behavioural deficits. Collectively, our findings elucidate a cell-type-specific circuit mechanism by which amygdala hyperactivity reshapes prefrontal inhibitory dynamics and neuropeptide release, driving mood-related deficits.

Disclosures: H. Wang: None. **M. Asim:** None. **J. He:** None.

Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

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Program #/Poster #: PSTR374.02/JJ4

Topic: H.05. Mood Disorders

Support: NIH Grant F30MH140515

Title: Dorsal striatum controls the development of social avoidance but not other depression-like behaviors after social defeat stress

Authors: *M. LIN[1], K. T. BEIER[2];
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Abstract: Depression is a heterogeneous disorder characterized by changes to cognitive, affective, somatic, and social functions. However, targeted treatments for this diverse array of symptoms are lacking largely because the neural circuit mechanisms underlying individual symptoms have yet to be clearly identified. Here, we use the social defeat stress (SDS) model in adult male C57Bl/6J mice to study three distinct stress-induced behavioral changes assessed by the social interaction, open field, and forced swim tests. Most studies investigating the neural circuitry underlying stress-induced behavior changes have grouped these broadly into one category of "depression-like behaviors", therefore losing this valuable symptom-specific granularity. Utilizing an unbiased, brain-wide c-Fos expression screen, we linked the putative activity of brain regions during the defeat experience to each distinct SDS-induced behavioral change. Unsurprisingly, we found relationships between amygdala activity and anxiety-like behavior in the open field test, as well as lateral orbitofrontal cortex (lOFC) activity and behavioral despair in the forced swim test. We also identified an unexpected relationship between dorsomedial striatum (DMS) activity and social behavior in the social interaction test. Using chemogenetic manipulations, we demonstrated that activity of distinct cell populations in each of these identified brain regions during SDS is causally related to changes in individual behavioral domains. We found that inhibiting GABAergic cells of the central amygdala prevented the development of anxiety-like behavior alone. Inhibiting the predominantly glutamatergic cells of the lOFC prevented the development of behavioral despair alone. Lastly, inhibiting the D1-type DMS cells or activating the D2-type DMS cells both prevented the development of social avoidance. In conclusion, these results provide clear evidence that distinct cell populations control the development of distinct stress-induced behavioral changes arising from the same stressor and identify the dorsal striatum as an important brain region regulating social avoidance behavior, encouraging further investigation into its role in adaptive and maladaptive social function.

Disclosures: M. Lin: None. **K.T. Beier:** None.

Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

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Program #/Poster #: PSTR374.03/JJ5

Topic: H.05. Mood Disorders

Support: NIH Grant MH070727
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Title: Enhanced ERK activity extends ketamine's antidepressant effects by augmenting hippocampal neuroplasticity

Authors: *Z. Z. MA[1], E. T. KAVALALI[2], L. M. MONTEGGIA[3];
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Abstract: Major Depressive Disorder (MDD) is a prevalent mental disorder and one of the leading causes of disability worldwide. Clinical studies consistently show that a single low dose of ketamine, a non-competitive NMDAR antagonist, produces rapid (within hours) and sustained (up to a week) antidepressant effects in patients with MDD. However, because ketamine's efficacy wanes over time, repeated treatments are necessary to preserve its antidepressant effects, which increases the risk of adverse side effects. This highlights the urgent need for approaches to maintain ketamine's antidepressant action from a single dose. Hippocampal neuroplasticity is a key process for stress responses, antidepressant effects, learning, memory, and emotion regulation. Specifically, ketamine induces a unique form of homeostatic synaptic plasticity at CA1 synapses, closely linked to its antidepressant effects and dependent on BDNF/TrkB signaling. Recently, we found that this plasticity can be augmented by transiently increasing TrkB-dependent ERK activity through the pharmacological inhibition of dual-specificity phosphatase-6 (DUSP6), a suppressor of the ERK pathway. Inhibiting DUSP6 boosts AMPA receptor expression on the synaptic surface and promotes synaptogenesis in the CA1 region, leading to extended antidepressant-like effects of ketamine that last over a month. The selective deletion of TrkB in excitatory CA1 neurons abolishes these synaptic and behavioral effects induced by DUSP6 inhibition. Additionally, in the dentate gyrus, ketamine accelerates the maturation of adult-born neurons via an ERK-dependent mechanism, as evidenced by improved synaptic arborization and function, which is vital for maintaining ketamine's effects. Moreover, specifically enhancing ERK activity in adult-born neural progenitors also prolongs ketamine's antidepressant actions. Consistent with this, RNAseq analyses of ketamine-treated hippocampal neurons reveal a set of genes involved in synaptic function and formation following DUSP6 inhibition. Overall, these findings suggest that prolonging ketamine's antidepressant effects could be achieved by enhancing neuroplasticity in hippocampal circuits by targeting specific intracellular signaling pathways. Also, the work provides a mechanistic framework to help answer a central question in neuropsychiatry of how brief drug exposure leads to persistent synaptic, circuit, and behavioral changes.

Disclosures: Z.Z. Ma: None. **E.T. Kavalali:** None. **L.M. Monteggia:** None.

Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.04/JJ6

Topic: H.05. Mood Disorders

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Title: FGFR1 signaling promotes stress resilience through a Notch-BDNF pathway in the dentate gyrus

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Abstract: Major depressive disorder (MDD) is associated with hippocampal dysfunction, but the cell-signaling logic linking stress-responsive growth factor pathways to antidepressant behavior remains poorly defined. In this translational study, we asked whether fibroblast growth factor receptor 1 (FGFR1) in the dentate gyrus (DG) engages a neurogenic antidepressant program through Notch and brain-derived neurotrophic factor (BDNF). Subregional RNA-seq and immunohistochemistry of human postmortem hippocampi (MDD, n=6; controls, n=9; RNA-seq subset, n=3 MDD/6 control) identified selective upregulation of FGFR1 and FGFR signaling in the DG. In male mouse corticosterone and chronic unpredictable mild stress models, DG-specific deletion of Fgfr1 accelerated depressive-like phenotypes, including reduced sucrose preference and increased immobility, without major changes in locomotion or anxiety-like behavior. To define downstream signaling with temporal precision, we activated optogenetic FGFR1 in DG granule neurons using dark/light, EGFP, shRNA, and pharmacological controls. FGFR1 activation rapidly induced Notch1 and Notch target genes, followed by increased BDNF. Notch1 knockdown reduced downstream Notch targets as well as BDNF, placing Notch upstream of the BDNF response. Functionally, 12 h FGFR1 activation increased EdU+ cells in the subgranular zone, and this neurogenic effect was blocked by the TrkB inhibitor ANA-12 or the Notch inhibitor DAPT, indicating that BDNF-TrkB and Notch signaling are required for FGFR1-induced adult hippocampal neurogenesis (AHN). In FGFR1 conditional knockout mice exposed to corticosterone, repeated DG optoFGFR1 activation restored AHN and rescued depressive-like behavior. Together, these data identify a DG FGFR1-Notch-BDNF-AHN axis that promotes adult hippocampal neurogenesis and buffers stress-induced depressive phenotypes.

Disclosures: J. Shin: None. **H. Oh:** None. **W. Heo:** None.

Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.05/JJ7

Topic: H.05. Mood Disorders

Support: UF College of Medicine
McKnight Brain Institute
UF Department of Neuroscience

Title: Rescuing social deficits in a depression-relevant mouse model through non-aggressive social exposure

Authors: *A. COTELO[1], A. PENA[2], A. BELL[2], K. CALDARONE[2], D. SONI[2], M. FEBO[3], M. BEDENBAUGH[4], F. J. MARTINEZ-RIVERA[2];
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Abstract: Depression is associated with reduced motivation to socialize and can be exacerbated by chronic social stress. Reduced depressive symptoms and improved remission are linked to social engagement, yet the mechanisms underlying this are unknown, and many individuals still show insufficient responsiveness to current treatments. Exposure- and extinction-based therapies can reduce stress responses to conditioned triggers in other stress-related disorders, suggesting that structured, non-threatening social exposure may help reduce social avoidance following chronic stress. Here, we tested whether social extinction, defined as repeated exposure to a non-aggressive, but threat-associated, social stimulus, can rescue social deficits in a depression-relevant mouse model. Male C57BL/6J mice underwent chronic social defeat stress (CSDS) to induce depressive-like and social avoidance behaviors. Following CSDS, mice received repeated non-aggressive social exposure with a CD1 mouse during a social extinction phase. Mice were then assessed using behavioral tests of social interaction, fear-related and exploratory behavior, and social self-administration, followed by brain tissue collection for cellular and molecular analyses of neural activity, stress signaling, and dopamine receptor expression. Our findings suggest that social extinction reduces CSDS-induced social deficits. Specifically, CSDS-Ext mice showed reduced social avoidance and fear-related behavior, along with increased exploratory behavior. Ongoing analyses will characterize stress-related and dopaminergic mechanisms using whole-brain tissue clearing to assess cFos, a proxy for neural activity, together with dopamine receptor expression. These studies are complemented by functional magnetic resonance imaging to assess changes in functional connectivity and resting-state activity. Together, this work suggests that repeated non-aggressive social exposure may reduce social deficits following chronic social stress and provides a framework for identifying neural mechanisms through which social exposure improves depression-relevant behaviors.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.06/JJ8

Topic: H.05. Mood Disorders

Support: NIH NIDA grant DP1DA056018
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Title: Single chromatin fiber and transcriptomic profiling of the 'postpartum' mouse brain

Authors: *A. HARNETT[1], Y. ZHU[1], S. AKBARIAN[2];
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Abstract: Background: Pregnancy induces significant plasticity in the maternal brain, but it also presents a vulnerable period for neurological disease. Structural brain changes in mothers are often linked to hormones like estradiol and progesterone, with studies in rodents showing how these hormones drive neuroplasticity during the transition to motherhood. Similar changes are observed across both pregnancy and adolescence, periods marked by steroid hormone fluctuations. While much is known about brain structure and hormone dynamics, less is understood about the molecular and genomic plasticity of human neurons and glial cells during these hormonally-dynamic periods. This project aims to explore how ovarian hormone withdrawal during the early postpartum period affects the epigenetic landscape. Our study will provide crucial insights into the genomic mechanisms underlying brain changes during pregnancy and postpartum, including how gene regulation may influence psychiatric risk.Methods: We employ a hormone-simulated mouse model of pregnancy, with a ‘postpartum’ period relevant to human conditions. Following hormonal withdrawal, brain regions were harvested and nuclei isolated for long-read chromatin fiber-sequencing and transcriptomic profilingResults: Fiber-seq analysis of mouse hippocampus revealed pregnancy-stage-specific chromatin changes, with gene ontology analysis of postpartum samples showing enrichment of hormone-responsive pathways. ESR1 and PGR motif analyses indicated reduced hormone motif accessibility in the postpartum period, accompanied by decreased differential transcription factor footprinting at the remaining accessible sites.Conclusion:Hormonal fluctuations during the peripartum period drive alterations in chromatin accessibility within the ventral hippocampus. These changes are likely associated with hormone-responsive gene regulation. Future work will involve mapping candidate genes identified in our mouse model to human GWAS datasets for psychiatric disorders, identifying potential risk genes for postpartum mental health conditions

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

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Program #/Poster #: PSTR374.07/JJ9

Topic: H.05. Mood Disorders

Support: nih dirp ziamh002797

Title: Chronic Induced Anhedonia Disrupts Cortical Network Dynamics and Alters Network Sensitivity to holographic Perturbation

Authors: ***T. SILVA**[1], P. KELLS[2], K. SRINIVASAN[2], T. L. RIBEIRO[2], B. GIFFORD[2], Y. BIBINEYSHVILI[2], D. PLENZ[2];
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Abstract: Major depressive disorder with anhedonia is associated with elevated glucocorticoids and glutamatergic dysfunction. To investigate how this condition alters cortical network dynamics and their response to direct neuronal perturbation, we used a mouse model of depression induced by chronic corticosterone (CORT) exposure. Adult male mice (N=27) expressing calcium indicators in anterior cingulate/medial prefrontal cortex were imaged with high-speed two-photon microscopy and divided into three groups: NO CORT, CORT-SAL, and CORT-KET. Anhedonia, assessed by sucrose preference, rose significantly after three weeks of CORT exposure ($p<0.001$). What changed was the network's organization: pairwise neuronal correlations declined significantly during peak anhedonia in CORT animals (no change in NO CORT), and power-law scaling of neuronal avalanches, significantly disrupted during the anhedonic state and recovered after cessation of CORT in both CORT-SAL and CORT-KET groups. To probe network excitability across the depression-recovery trajectory, a separate CORT-KET cohort (N=5) underwent all-optical holographic stimulation at six time points: before CORT (baseD1), 18 days into CORT treatment, and 1 hour, 1 day, 3 days , and 9 days after a single subanesthetic ketamine dose. Neurons were classified as positive responders, negative responders, or non-responders relative to their spontaneous baseline (z-test, $\alpha=2.5\%$, one-tailed). At ketD0 after ketamine, the network's reaction to perturbation sharpened. The number of neurons falling silent (negative responders) rose dramatically across all targets and animals ($p=4.4\times10[^{-}11]$), lowering the background firing against which an evoked response is read, while the number of neurons firing in the expected, stimulus-driven direction (positive responders) increased more modestly but significantly ($p=2.7\times10[^{-}2]$). Mean pairwise correlations continued to decline through cortD18 and ketD0, then progressively recovered over the following nine days. We conclude that chronic induced anhedonia impairs both spontaneous and stimulus-driven cortical dynamics in the frontal cortex, pushing the network out of its critical state. One hour after a single dose, ketamine reshapes how the network answers a focal input: more neurons go quiet while a smaller set is recruited into the expected response. Ketamine turns down the background chatter and lets the targeted signal stand out, raising the signal-to-noise of cortical reactivity. This contrast-enhancing reconfiguration offers a network-level account of how a rapid antidepressant restores the frontal cortex's capacity to respond selectively to input.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR374.08/JJ10

Topic: H.05. Mood Disorders

Title: Neural activity in the mouse frontal cortex following allopregnanolone administration

Authors: *A. D. GILBERT[1], A. KWAN[2];
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Abstract: Postpartum depression is a debilitating condition affecting approximately 15% of women. It is associated with increased mortality risk and long-term effects on the wellbeing of both mother and child. In 2019, brexanolone became the first FDA-approved medication for postpartum depression. Brexanolone is an intravenous formulation of allopregnanolone, which is a naturally occurring neuroactive steroid and a positive allosteric modulator of extrasynaptic GABA-A receptors. The current therapeutic rationale of this treatment is to restore allopregnanolone levels that sharply drop postpartum. However, it is largely unclear how allopregnanolone alters brain function. The goal of the current study is to investigate the effects of allopregnanolone administration on behavior and neural activity. We started by characterizing the behavioral effects of allopregnanolone in female C57BL/6J mice. In the open-field test, we found that allopregnanolone increases locomotor activity at moderate doses, but decreases locomotor activity at higher doses. The sedative effect is consistent with allopregnanolone acting as a positive allosteric modulator of the GABA-A receptor. Next, we determined the effects of allopregnanolone on the activity dynamics of excitatory and inhibitory neurons. Using a high-density Neuropixels 1.0 probe, we recorded spontaneous spiking activity in the medial frontal cortex of awake, head-fixed female mice. We recorded from PV-Cre;Ai32 mice, where PV interneurons express channelrhodopsin, allowing us to identify recorded units that are PV interneurons. Briefly, we recorded baseline spiking activity for 30 min, administered allopregnanolone (10 mg/kg) or vehicle intraperitoneally through a catheter, and recorded post-injection activity for 60 min. At the end of each session, 473 nm light pulses were delivered through an optical fiber to identify PV interneurons. Single units were identified by automated spike sorting followed by manual curation. We quantified the firing rates of PV interneurons and untagged, putative excitatory cells, comparing the activity levels before and after drug administration. Our results suggest that allopregnanolone may acutely alter the balance of activity in excitatory and inhibitory neurons in the frontal cortex.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.09/JJ11

Topic: H.05. Mood Disorders

Support: BD2

Title: Cell-type targeted CRISPR/Cas9 Clock knockdown in mouse VTA dopamine neurons alter sleep, behavior, and cellular excitability

Authors: *Y. JU[1], J. ZHAO[3], S. SIANATI[6], C. EGEBJERG[7], O. C. GONZALEZ[9], A. CRISWELL[1], C. LEE[1], K. DU[4], C. E. LUFF[8], J. STRALKA[7], V. KNAPP[10], L. DE LECEA[11], Y. KOZOROVITSKIY[5], J. A. KAUER[7], L. E. FENNO[2];
[2]Psychiatry & Neurosci., [1]Univ. of Texas at Austin, Austin, TX; [3]Northwestern Univ., Chicago, IL; [5]Neurobio., [4]Northwestern Univ., Evanston, IL; [6]Psychiatry and behavioral Sci., [7]Stanford Univ., Stanford, CA; [8]Psychiatry and Behavioral Sci., Stanford Univ., Portola Valley, CA; [9]Dept. of Integrative Physiol., Univ. of Colorado Boulder, Boulder, CO; [10]Dept. of Psychiatry & Behavioral Sciences, Stanford Univ. Sch. of Med., Stanford, CA; [11]Psychiatry, Stanford, Stanford, CA

Abstract: Bipolar disorder (BD) is a severe psychiatric disease characterized by recurrent mania, depression, and circadian rhythm disruption. Among circadian regulators implicated in mood-related dysfunction, Clock has emerged as a particularly strong mechanistic candidate. However, cell type-specific functions of Clock within mood-relevant circuits remain incompletely defined. Here, we developed and applied a Cre-dependent AAV-SaCas9 gene-editing strategy to disrupt Clock selectively in ventral tegmental area dopamine neurons. We first established a rapid *in vitro* screening pipeline for guide RNA selection that accurately predicted *in vivo* editing efficiency. We then targeted Clock *in vivo* using a single AAV-based editing strategy and observed robust titer-dependent reduction of Clock expression, by targeted sequencing, *in situ* hybridization, and immunohistochemistry. We assessed the functional consequences of Clock disruption across analysis levels, including a behavioral battery, circadian and sleep-wake measurements using EEG and EMG, and electrophysiological recordings. These results establish a practical framework for rapid, cell-type-specific disruption of candidate psychiatric risk genes and provide a mechanistically grounded model for investigating how loss of Clock function in mesolimbic dopaminergic circuits contributes to BD-relevant phenotypes.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.10/JJ12

Topic: H.05. Mood Disorders

Support: MH106460

Title: Circadian Regulation of HDAC2 Chromatin Binding in the Ventral Tegmental Area of ClockΔ19 Mice

Authors: *M. KAMINSKY[1], R. YIN[1], N. FAIRBANKS[1], C. A. MCCLUNG[2];
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Abstract: Bipolar disorder (BD) is a common mood disorder associated with disruptions in circadian rhythms. One of the most prescribed treatments for acute mania is the anticonvulsant valproate (VPA); however, it is associated with side effects and variable efficacy. VPA has multiple molecular targets, including histone deacetylases (HDACs). Using ClockΔ19 mice, a model carrying a dominant-negative mutation in the Clock gene that exhibits mania-like behaviors, we have previously shown that selective knockdown of HDAC2 in the ventral tegmental area (VTA) normalizes these behaviors, similar to VPA treatment. In a pilot CUT&RUN study, we identified HDAC2-associated genomic regions in the VTA linked to BD relevant pathways. Here, we expand on this work to investigate whether HDAC2 chromatin binding is circadian and whether its rhythmicity differs by genotype (ClockΔ19 vs WT) and sex. ClockΔ19 and WT male and female mice (n = 6 per time point, sex, and genotype) were sacrificed at 6 time points across the 24-hour cycle. Brains were rapidly extracted and flash-frozen, VTA tissue was micro dissected. CUT&RUN was performed using the Cell Signaling CUT&RUN kit, followed by library prep and sequencing at the University of Pittsburgh Genomics Core. Peaks were identified using SEACR. We identified 460 rhythmic HDAC2 peaks in WT mice and 401 in ClockΔ19 mice, with only 18 peaks shared between genotypes. Peak timing distributions spanned the full circadian cycle in both groups but exhibited clear phase differences, with WT peaks enriched earlier in the light phase and ClockΔ19 peaks shifted toward later timepoints. Differential binding analysis revealed modest but consistent genotype effects, with more HDAC2-enriched regions in ClockΔ19 compared to WT (Day: 49 vs 15; Night: 66 vs 16 peaks at $p < 0.05$ and $|\log2FC| \geq 1.5$). Sex-specific effects were more pronounced during the daytime (89 female-biased vs 4 male-biased peaks) and more balanced at night. These findings demonstrate that HDAC2 binding in the VTA is highly circadian, with the ClockΔ19 mutation leading to a shift in binding phase and a reorganization of chromatin occupancy patterns. This temporal dysregulation of HDAC2 targeting may contribute to altered gene regulation underlying mood-related phenotypes in bipolar disorder.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.11/JJ13

Topic: H.05. Mood Disorders

Support: Breakthrough Discoveries for Thriving with Bipolar Disorder DG240716

Title: Investigating the Role of Cerebello-Thalamocortical Pathway Dysfunction in Bipolar Disorder

Authors: *F. XU[1], L. YANG[2], J. Q. PAN[3];
[1]Broad institute, Cambridge, MA; [2]Broad Inst., Belmont, MA; [3]Stanley Ctr. for Psychiatric Res., Broad Inst., Cambridge, MA

Abstract: Bipolar disorder (BD) is a severe psychiatric illness characterized by biphasic mood episodes of mania and depression. Recent human exome sequencing studies have identified Akap11 as a risk gene for BD. Akap11 mutant mice recapitulates key electrophysiological phenotypes observed in patients, including reduced NREM sleep and decreased sleep spindle density. The thalamic reticular nucleus (TRN), a GABAergic regulator of thalamocortical activity plays a critical role in sleep regulation, while cerebellar dysfunction has also been implicated in BD. However, the contribution of the these circuits to BD remains unclear. We hypothesize that dysfunction in cerebellum and thalamocortical circuit contributes to altered sleep and affects in BD. We used an Akap11 loss-of-function (LoF) mouse model and performed ex vivo whole-cell patch-clamp recordings in brain slices to characterize neuronal properties in the TRN and cerebellum. In cerebellar Purkinje cells, Akap11 KO mice exhibited impaired high-frequency firing, along with reduced action potential (AP) full width at half maximum (FWHM) and afterhyperpolarization (AHP) amplitude. Notably, sag responses were also altered, suggesting dysregulation of HCN channel-mediated currents. In addition, TRN neurons of Akap11 KO mice showed enhanced rebound bursting, an increased number of rebound bursts following hyperpolarization, and a reduced tonic firing rate. Together, these findings indicate that Akap11 Lof alters intrinsic excitability in both cerebellar and thalamic circuits, potentially mediating sleep-related and affective processes that are important in BD. This study highlights the role of TRN and cerebellum impairment in linking genetic risk to circuit dysfunction in BD.

Disclosures: F. Xu: A. Employment/Salary (full or part-time):; Broad institute. **L. Yang:** A. Employment/Salary (full or part-time):; Broad institute. **J.Q. Pan:** A. Employment/Salary (full or part-time):; Broad institute.

Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.12/JJ14

Topic: H.05. Mood Disorders

Title: The Role of Extracellular Matrix and Integrins in the Prefrontal Cortex of Major Depression: Insights from Cyr61 and ItgaV

Authors: *A. B. COOK[1], E. M. PARISE[2];
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Abstract: Major depression is a complex psychiatric disorder characterized by dysregulated molecular pathways. Recent research has underscored the pivotal role of the prefrontal cortex (PFC) in depression, with particular emphasis on the involvement of the extracellular matrix (ECM) and integrins in PFC dysfunction. Cyr61, a secreted matricellular protein, governs a wide array of cellular processes and directly engages with integrins and heparan sulfate proteoglycans, thereby triggering intracellular signaling cascades. The integral membrane protein ItgaV, an integrin subunit, operates in cell surface adhesion and signaling and is known to interact with Cyr61. Consequently, this study was designed to investigate the involvement of the ECM and integrins in depression by scrutinizing the expression of Cyr61 and ItgaV mRNA in mice exposed to distinct stress paradigms, as well as in patients diagnosed with major depressive disorder (MDD). Our findings reveal that male, but not female, MDD patients exhibited a significant reduction in Cyr61 and ItgaV mRNA expression within the PFC compared to controls, underscoring their potential relevance in the context of depression in humans. Similarly, Cyr61 mRNA expression was downregulated in the PFC of both male and female mice exposed to chronic variable stress (CVS) and in chronic social defeat stress (CSDS)-exposed susceptible mice, implicating its role in stress-induced depressive-like behaviors. In contrast, while a substantial downregulation in ItgaV mRNA was observed in the PFC of CSDS-exposed susceptible mice, no change in ItgaV mRNA was detected in mice exposed to CVS. Notably, we identified a positive correlation between Cyr61 and ItgaV mRNA expression in the PFC of both CSDS-exposed mice and human subjects, suggesting their potential co-participation in depression-related molecular mechanisms. In summary, the disruption of Cyr61 and ItgaV mRNA expression patterns within the PFC underscores their pivotal roles in MDD. Moreover, these findings underscore the significance of comparing various stress models to select the most clinically relevant approach based on molecular insights in humans. A deeper understanding of the interplay between ECM, integrins, and Cyr61 within the PFC holds promise for providing valuable insights into the development of innovative therapeutic strategies targeting these pathways for the treatment of major depression.

Disclosures: A.B. Cook: None. **E.M. Parise:** None.

Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

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Program #/Poster #: PSTR374.13/JJ15

Topic: H.05. Mood Disorders

Support: BB/V015028/1
MR/X010910/1
MR/L011212/1

Title: Novel Insights into the Neuropsychological Effects of Serotonergic Psychedelics and Their Underlying Molecular and Circuit Mechanisms

Authors: ***M. CLAYDON**[1], J. K. HINCHCLIFFE[2], J. BARTLETT[1], C. GOLDEN[3], C. THOMAS[3], G. GILMOUR[3], J. R. MELLOR[4], Z. A. BORTOLOTTO[1], E. S. ROBINSON[1]; [2]Sch. of Physiology, Pharmacol. and Neurosci., [1]Univ. of Bristol, Bristol, United Kingdom; [3]COMPASS Pathways Plc, London, United Kingdom; [4]Univ. Bristol, Bristol, United Kingdom

Abstract: Negative affective biases are important neuropsychological features of depression modulated by conventional and rapid-acting antidepressants (RAADs). Previous studies suggest the time course of clinical effects of different antidepressants are related to distinct neuropsychological effects. Conventional antidepressants bias new experiences while RAADs modulate negative biases associated with past experiences. With growing interest in the therapeutic potential for psychedelics in psychiatry, this study first characterised the effects of different serotonergic psychedelics in our translational rat affective bias test. To investigate the mechanisms which underlie affective bias modifications by psilocybin we combined our behavioural studies with targeted brain manipulations and expression of an inhibitory DREADD within cortico-amygdala (CA) neurones. We also used ex vivo electrophysiology to characterise the effects of psilocybin in tracer labelled subpopulations of layer 5 prefrontal cortical neurones.The effects of the psychedelics varied in terms of the different neuropsychological mechanisms associated with affective bias modification. Psilocybin attenuated negatively biased memories and facilitated re-learning of past experiences with a more positive affective valence and positively biased new learning. Of the other psychedelics tested, only MDMA specifically attenuated retrieval of a negatively biased memory. LSD attenuated the negative bias at higher doses but had non-specific effects. At 24hrs post treatment N,N-DMT had sustained effects but only psilocybin facilitated re-learning with a more positive affective valence. However, like psilocybin and conventional antidepressants, N,N-DMT positively biased new experiences. Further characterisation of psilocybin's behavioural effects identified the prelimbic subregion of medial prefrontal cortex (PrL) as a key locus, and the electrophysiology experiments revealed a cell-type-specific regulation of synaptic transmission. Acute psilocin selectively suppressed excitatory synaptic input to CA projection neurons and 24hr post-treatment enhanced inhibitory synaptic input selectively in CA cells. Chemogenetic inhibition of CA neurons in PrL recapitulated the effects of psilocybin.These findings suggest there are distinct neuropsychological effects associated with different psychedelics which may be relevant to their efficacy in treating emotional disorders. We also identify modulation of the PrL cortico-amygdala circuit as a key substrate for affective bias modification by psilocybin, an effect which could explain its antidepressant effects.

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Pathways ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); G.G. holds shares in COMPASS Pathways ltd and Eli Lilly & Co. Ltd. **J.R. Mellor:** None. **Z.A. Bortolotto:** None. **E.S. Robinson:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); E.S.J.R. has obtained research funding from Boehringer Ingelheim, Compass Pathways ltd, Eli Lilly, IRLab Therapeutics, MSD, Pfizer, and Small Pharma..

Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.14/JJ16

Topic: H.05. Mood Disorders

Title: Beyond the head twitch response: more effective tracking of psilocybin pharmacodynamics in rats with behavioural and electrophysiological measures

Authors: C. THOMAS[1], D. ANDERSON[2], E. KOLESNIK[4], V. SHALGUNOV[5], M. HERTH[6], T. BLACKMORE[1], C. GOLDEN[1], L. WRAY[1], M. PALNER[7], E. S. ROBINSON[3], ***G. GILMOUR**[1];
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Abstract: Psychedelics are well known to induce head twitch response (HTR) behaviours most prominently in mice. While a useful indicator of psychedelic propensity, HTR is much less reliable when assessing pharmacokinetic/pharmacodynamic (PK/PD) relationships in rats. This work combined behavioural and electrophysiological methods to address this problem, using COMP360 (Compass' proprietary synthetic crystalline form of psilocybin) as an exemplar compound.Plasma and brain PK of doses of 1mg/kg psilocybin via subcutaneous (sc) and oral (po) routes was measured in male Sprague Dawley rats. Relative to po, sc dosing produced earlier and greater maximal psilocin concentrations with shorter terminal half-lives. $5HT_{2A}$ receptor occupancy (RO) following psilocybin dosing (0.1 - 3 mg/kg sc at 70 min; 1 mg/kg sc from 15 - 360 min) was measured in male Long Evans rats using the antagonist ligand [^{18}F]MHMZ. Psilocin RO was dose-dependent across the 0.1 - 3 mg/kg dose range and maximal at 3 mg/kg. At 1 mg/kg sc, peak occupancy was measured 15 min after administration and subsequently declined in alignment with psilocin plasma terminal half-life.HTR was measured in male Sprague Dawley rats following doses of 0.1 - 30 mg/kg sc psilocybin. Significant increases in HTR were found only at 0.3 mg/kg, with a time course that did not match the psilocin plasma concentration-time profile. Instead, a measure of task engagement using a variable interval 30 s (VI30) instrumental response task in male Lister Hooded rats demonstrated that across a dose range of 0.1 - 3 mg/kg sc psilocybin, significant decreases in VI30 task responding were very

clearly dose- and route-dependent. The temporal profile of VI30 task disengagement correlated with psilocin exposure. Finally, frontoparietal cortical EEG recording in male Sprague Dawley rats revealed dose- and route-dependent changes in parietal cortex activity, characterised by reduced low-alpha (7-9 Hz) and gamma (30-100 Hz) power, and increased low-theta activity (4-6 Hz). Reduction in gamma and low-alpha power closely tracked psilocin exposure, whereas low-theta elevation was delayed, beginning only after drug exposure peaked. Effects of oral psilocybin tended to occur only at higher doses, demonstrating a shifted dose-response curve as also observed in the VI30 task. Cortical EEG measures provide information that complements both psilocin plasma and brain exposure measures and psychedelic-induced changes in behavioural state. Altogether the integrated behavioural and electrophysiological approach demonstrated here offers much more opportunity to learn more about comparative duration and quality of novel psychedelic drug effects in rats.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.16/JJ18

Topic: H.05. Mood Disorders

Title: Integrated Molecular and Neurohistological Spatial Biomarker Mapping of Altered Synaptic Plasticity in Rodent Models of Depression

Authors: *E. PASCHEN, M. PALMAS, C. J. MALTBY, A. MOREIRA DE SA, E. LIUBISHKIN, D. SELLERI, J. PINTO, M. BIANCHI;
Ulysses Neurosci. Ltd., Dublin, Ireland

Abstract: Background: Depression remains a major global health challenge driven in part by neuroinflammation and impaired neuronal plasticity. We previously demonstrated that chronic interferon-alpha (IFN-alpha) administration in Wistar Han rats, and the Wistar Kyoto (WKY) rat as an innate model of SSRI-resistant depression, produce robust depressive-like phenotypes accompanied by disrupted microtubule dynamics and reduced synaptic protein expression. Here, we extend these findings through integrated spatial biomarker mapping, combining Golgi-Cox staining and immunohistochemistry (IHC) to characterise region-specific structural and molecular alterations in synaptic plasticity across both models, and to assess restoration by the neuroplastogens ketamine and psilocybin. **Methods:** Golgi-Cox staining was applied to brain tissue from IFN-alpha-treated Wistar Han rats to quantify dendritic spine density and morphology in the mPFC and hippocampus. IHC was performed in both IFN-alpha-treated rats and WKY rats to spatially map expression of pre- and post-synaptic markers (SV2A, synaptophysin, PSD-95, spinophilin) and alpha-tubulin as indices of microtubule dynamics. The effects of acute ketamine (5 mg/kg, SC) and psilocybin (1 mg/kg, SC) on these endpoints were assessed relative to vehicle controls 24h post-administration. **Results:** IFN-alpha treatment produced region-specific reductions in dendritic spine density and alterations in spine morphology in the mPFC and hippocampus. IHC revealed region-specific deficits in pre- and post-synaptic protein expression alongside a shift in alpha-tubulin PTMs towards a more stable microtubule state in both IFN-α-treated rats and WKY rats. Acute ketamine and psilocybin produced region-specific normalisation of synaptic marker expression and alpha-tubulin PTM balance in both IFN-alpha-treated rats and WKY rats. In IFN-alpha rats, Golgi-Cox staining additionally confirmed restoration of dendritic spine density and morphology. **Conclusions:** These data provide the first integrated neurohistological and molecular spatial biomarker map of synaptic plasticity deficits in the IFN-alpha and WKY models of depression, and demonstrate that neuroplastogens can reverse these structural and molecular signatures. This approach strengthens the translational relevance of these preclinical models and supports the use of spatially resolved biomarkers to evaluate fast-acting antidepressant candidates targeting neuroplasticity.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.17/JJ19

Topic: H.05. Mood Disorders

Title: A frustrative nonreward paradigm modulates acetylcholine dynamics in the nucleus accumbens

Authors: *H. COATL-CUAYA, Z. LI;
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Abstract: The negative emotional reaction to the unexpected omission of a reward is known as frustrative nonreward (FNR). This phenomenon triggers irritability, which is characterized by a low threshold for anger and frustration and has been included in the DSM-5 as a feature of disruptive mood dysregulation disorder (DMDD). Irritability is prevalent across all ages but is particularly pronounced among youth, and evidence suggests that chronic irritability might be a contributor to psychiatric disorders such as depression, anxiety, and addiction in adulthood. Hyperlocomotion and aggression are behavioral signs of FNR across species. While several brain regions contribute to reward processing, the nucleus accumbens (NAc) is crucial for integrating learning with reward and goal-motivated behaviors. Although more than 90% of the neuronal population in the NAc consists of GABAergic medium spiny neurons (MSNs) expressing D1 and D2 dopamine receptors, there is a small population (~5-10%) of cholinergic interneurons (CINs). These CINs are believed to modulate NAc activity by releasing acetylcholine (ACh), which acts on MSNs and can influence presynaptic dopamine release. This mechanism may play a role in driving behavioral outcomes, and little is known about cholinergic dynamics in the NAc during FNR. This study aimed to investigate the activity of CINs and Ach release under an FNR paradigm. We introduce C57BL/6J and ChAT-IRES-Cre mice (P48-56) to the alternate poking reward omission (APRO) task, a FNR paradigm previously developed in our lab. At three weeks old, the animals underwent stereotaxic injections of AAV-hSyn-GRAB_ACh3.0 and AAV-syn-FLEX-jGCaMP8m-WPRE and cannula implantation in NAc for fiber photometry recordings. 4-6 weeks post-injection, mice were put on water restriction and trained for 4 days to visit two ports alternately to obtain water. Reward was omitted in 50%, and then 80% of correct alternation trials in subsequent sessions. Our results show that animals increase the total number of visits to the ports during reward omission trials, especially on 80% of reward omission days. The imaging results showed a synchronized activation of CINs and Ach release during reward trials, followed by a transient suppression. Interestingly, reward omission trials presented a non-synchronized activity of CINs and Ach release. Our data provides insights into how CINs and Ach of the NAc are influenced by FNR. These results may contribute to the understanding of reward-omission processing during frustration.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.18/JJ20

Topic: H.05. Mood Disorders

Support: P50MH136297

Title: The anterior insular cortex mediates higher order threat learning and memory through distinct ensembles

Authors: H. NAMKUNG[1,3], ***B. MUKHERJEE**[4], I. MIURA[2], A. SAITO[4], K. ISHIZUKA[2], H. KWON[5], A. SAWA[2,6,7,5,4];
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Abstract: Learning to anticipate and respond to potential threats is crucial for survival; dysregulation of these cognitive processes is a core hallmark of neuropsychiatric conditions. While human neuroimaging frequently implicates the anterior insular cortex (AIC) in threat processing, its precise causal circuit mechanisms remain poorly defined, fundamentally limiting the development of targeted therapeutics. Using multimodal systems neuroscience in mice, including in vivo fiber photometry (GCaMP6f), cell-type and projection-specific optogenetics (eNpHR3.0, eOPN3), chemogenetics, and ST-Cal-Light activity-dependent tagging, we dissected the role of the AIC in associative threat learning paradigms of varying cognitive demand. We found that AIC excitatory layer 5 pyramidal neurons (L5-PNs) are not needed for simple, associative threat learning (Delay Fear Conditioning). However, they are essential for complex threat processing that involves temporal or contextual uncertainty. In Trace Fear Conditioning, where a silent gap separates the warning cue from the threat, fiber photometry showed a growing calcium signal in AIC L5-PNs that acts as a bridge across this silence. Viral tracing and targeted optogenetics confirmed these specific neurons form a specialized, BLA-projecting output pathway. Furthermore, in Contextual Fear Conditioning, the AIC plays a dual role: it acts as the fuel to build the memory during learning, but switches to act as a brake to control fear expression during recall. Using dual-labeling techniques, we discovered that these two opposite tasks are handled by largely non-overlapping neuronal ensembles within the AIC. These findings show that the AIC is essential for predicting and managing uncertain threats. By revealing that largely distinct neuronal populations in this circuit are responsible for building fear versus keeping it in check, our work bridges a critical knowledge gap in threat processing. Instead of relying on broad regional models, mapping these distinct microcircuits uncovers highly specific anatomical targets.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.19/JJ21

Topic: H.05. Mood Disorders

Support: NIH R21 MH135207
2024 NARSAD Young Investigator's Award

Title: Utilizing visual stimuli to promote selective plasticity in Nucleus Accumbens D1-MSNs

Authors: *E. LEE[1], D. RATNA[1], T. FRANCIS[2];
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Abstract: Current pharmacological treatments for depression are often ineffective for about 30% of patients. Among the therapeutics for treatment resistant depression, the gold standard therapy is transcranial magnetic stimulation (TMS), a non-invasive brain stimulation therapy, which targets the prefrontal cortex to reverse cortical hypoactivity. TMS typically requires an extensive number of sessions and weeks for therapeutic efficacy, highlighting a critical need for faster-acting options for treatment resistant individuals. Previous findings in mice indicate that chronic stress reduces activity in the prefrontal cortex (PFC) and decreases excitatory transmission to Nucleus Accumbens (NAc) dopamine 1 (D1) receptor medium spiny neurons (MSNs), a cell type that is necessary for the expression of anhedonia. We have discovered that flashing non-red light into the eyes of mice can selectively activate NAc D1-MSNs in both awake and anesthetized states. Based on systemic and local NAc pharmacology, these responses are dependent on NMDA receptor and dopamine 1 receptor activation. Since NMDA receptors are critically involved in the induction of post-synaptic excitatory plasticity, and are necessary for sustained depolarization in MSNs, we predicted that this light flash-evoked event could open a window for spike-timing dependent plasticity selectively in D1-MSNs. We found that timed light flashes delivered prior to PFC optogenetic stimulation primarily increases *in vivo* excitatory responses on D1-MSNs, but pairing light after the optogenetic stimulation primarily decreases excitatory responses on D1-MSNs. Surprisingly, pairing light flashes prior PFC optogenetic stimulation promoted long-term depression in D2-MSNs, despite light flash insensitivity. We are currently testing other timings in animals that have undergone chronic stress or stress-naïve mice to determine if we can reverse maladaptive outcomes on excitatory transmission after repeated stress. These results may provide a novel therapeutic method for rebalancing excitatory transmission to NAc D1-MSNs in depressed individuals and may provide a method to promote more rapid acting anti-depressant efficacy in TMS treatment for depression.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.20/JJ22

Topic: H.05. Mood Disorders

Support: NIH Grant F32MH125597
W.M. Keck Foundation
Max Planck Florida Institute for Neuroscience

Title: Endogenous serotonin activity during fear conditioning is best described by temporally distinct release patterns that predict behavior

Authors: *E. C. WRIGHT[1], J.-Y. MIN[2], L. TIAN[2];
[1]Tian Lab., [2]Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: Serotonin (5-HT) is a key neuromodulator coordinating emotional affect and behavioral output, and disruptions to 5-HT function are implicated in diverse neuropsychiatric disorders. Despite widespread use of serotonergic therapeutics, efficacy varies substantially across individuals, and mechanistic understanding remains limited. A core barrier is the lack of characterization of endogenous 5-HT release at behaviorally relevant timescales. Without this baseline, pharmacological interventions lack a reference for interpreting or restoring healthy function. Using the genetically encoded sensor iSeroSnFR2.0, we recorded endogenous OFC 5-HT release in male C57Bl/6 mice during auditory cued fear conditioning and extinction.
We employed an audio-cued fear conditioning paradigm across 4 days that consisted of distinct baseline (tone only), conditioning (tone co-terminates with footshock), and extinction (tone only) conditions. Freezing during tone presentation was used as a quantifiable expression of fear state. Principal component analysis decomposed 5-HT signals into three temporally distinct patterns: two anxiogenic tone-onset components (sustained and phasic) tracking anticipated threat, and a post-shock component tracking experienced aversive outcome. Fear strength bidirectionally modulated these patterns: low-shock mice (0.3mA, n=11) showed suppressed 5-HT components, reduced freezing, and weakened 5-HT-freezing coupling relative to high-shock mice (1.7mA, n=12). Acute fluoxetine (20mg/kg in drinking water, 24hr prior + throughout testing) or optogenetic activation of dorsal raphe (n=10) in low shock mice both enhanced anticipatory 5-HT features and increased freezing, establishing bidirectional causal relationships between 5-HT release structure and fear behavior.
Chronic fluoxetine (20mg/kg in drinking water, 4 weeks + throughout testing, n=11) selectively suppressed tone-onset patterns while sparing the post-shock component. This selective remodeling—dampening anticipatory while preserving outcome-related signaling—decoupled the predictive relationship between 5-HT release and freezing and was associated with reduced fear acquisition and enhanced extinction. All comparisons used linear mixed-effects models with mouse identity as a random effect.
These findings establish that the temporal structure of OFC 5-HT release, not overall magnitude, predicts fear behavior, and that antidepressant treatment converges on selective remodeling of anticipatory 5-HT signaling as a behaviorally relevant mechanism.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.21/JJ23

Topic: H.05. Mood Disorders

Support: This work was supported by the Stanley Center for Psychiatric Research
Harvard Brain Science Initiative Bipolar Disorder Seed Grant

Title: Elevated synaptic PKA activity and abnormal striatal dopamine signaling in Akap11 mutant mice, a model of bipolar disorder

Authors: *B. J. SONG[1], Y. GE[2], B. LODDER[4], M. CHEN[5], N. D. HARTLEY[8], C. GENG[6], S. NATARAJAN[5], A. HALL[14], J. TIAN[9], S. ARYAL[10], X. LIU[15], H. PRIBIAG[11], S. SIMMONS[3], B. A. STEVENS[16], P. S. KUNWAR[7], Z. FU[15], E. MACOSKO[12], B. L. SABATINI[17], B. DEJANOVIC[18], A. J. GRANGER[13], M. H. SHENG[19];
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Abstract: Loss-of-function mutations in AKAP11 (a protein kinase A (PKA)-binding protein) greatly increase the risk of bipolar disorder and schizophrenia. We conducted multi-omic analyses of Akap11 mutant mouse brains and reported the neurobiological functions of AKAP11 and the consequences of its absence. AKAP11 interacts with multiple proteins involved in signaling and proteostasis. In Akap11+/- and Akap11-/- synapses, PKA protein levels were markedly elevated, and many synaptic proteins were hyperphosphorylated at PKA substrate sites. Akap11 mutant brains showed extensive transcriptomic changes, prominently in synapse-related gene-sets and most profoundly in neurons of the striatum, a brain region implicated in motivation, cognition and psychiatric disorders. Spatial transcriptomics analysis reveals topologically organized and cell-type specific impact to spiny projection neurons of the Akap11 mutant striatum. In vivo, real-time measurements of PKA activity in Akap11-/- revealed constitutively elevated kinase activity, which distorts the dynamic range of dopamine to PKA signaling in the striatum. Our work reveals the molecular basis of circuit dysfunction in a genetically valid model of psychotic disorder.

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Poster

PSTR374: Neural Mechanisms of Stress and Depression in Animal Models

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.22/JJ24

Topic: H.05. Mood Disorders

Support: T32 NS-45540

Title: Investigating neural signatures of resilience and susceptibility to social defeat in mice

Authors: *J. MOORE[1], M. LIN[3], K. BEIER[2];
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Abstract: Depression is among the most common mental health conditions in the world, with symptoms that can vary widely between cases, including anhedonia, low energy, and/or social isolation. Despite the prevalence and societal impacts of depression, much remains unknown about how depression manifests, and what the neural signatures of depression-associated brain dysfunction are. Using social defeat stress as a model of stress-induced depressive-like symptoms, we are studying the neural activity signatures of susceptibility and resilience to defeat-induced phenotypes in subcortical structures. Using Neuropixels high-density arrays, we are exploring neural activity patterns that relate to depression-related phenotypes that manifest in the brains of defeated mice, as well as those that exist in a pre-defeated state that relate to susceptibility or resilience states. Further, we are using Consistent EmBeddings of high-dimensional Recordings using Auxiliary variables (CEBRA) to map the trajectory of neural signatures that define susceptibility states. We have found robust signatures of neural activity that relate to behavioral signatures, with the identity of these features differing by brain region. Further, latent structure identification through dimension reduction also showed that the baseline neural activity could be a strong predictor of susceptibility/resilience. These results show that baseline neural activity may contain specific biomarkers that can predict stress vulnerability and depressive-like phenotype in mice.

Disclosures: J. Moore: None. **M. Lin:** None. **K. Beier:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.01/KK1

Topic: H.08. Drugs of Abuse and Addiction

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Title: Developing the dopamine D3 receptor (D3R) antagonist, (R)-VK4-116, as a non-opioid medication for the treatment of opioid use disorder

Authors: ***Y.-C. LIN**[1], C.-K. WU[1], S. MOUNAUD[1], M. CONGDON[1], R. NANDRE[1], B. DING[1], J. HUANG[1], H. JIN[1], P. TERSE[1], K. SHEN[1], G. TAWA[1], P. SANDERSON[1], M. DE SANTIS[2], D. LO[4], E. OTTINGER[1], A. H. NEWMAN[3];
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Abstract: Opioid use disorder (OUD) affects millions of adults worldwide. Despite the availability of three approved medications for treating OUD (methadone, buprenorphine and naltrexone), all of which target opioid receptors, side effects, compliance and access remain challenges that confound recovery. Consequently, there is a need for new medicines to treat OUD that may also have the potential to combat a variety of substance use disorders (SUD), as polydrug misuse is common. The dopamine D3 receptor (D3R) plays a pivotal role in reward, the development of drug dependence, and impulse control. Computational models based on the x-ray crystal structure of D3R in complex with a D2R/D3R antagonist, eticlopride, together with small molecule structure-activity relationships, inspired the design and synthesis of the highly D3R-selective antagonist (±)VK4-116. (±)VK4-116 is effective in mitigating the behavioral effects of opioids across multiple OUD models in rodents, while having no rewarding effects of its own. Moreover, (±)VK4-116 enhances the effectiveness of opioid analgesics and also mitigates long-term cognitive deficits induced by chronic cocaine use. Based on these findings, the eutomer, (*R*)-VK4-116, was assessed as a preclinical development candidate and completion of investigational new drug (IND) enabling studies were conducted in collaboration with NIDA and NCATS. A multi-kilogram scale GMP synthesis, formulation for maximized oral bioavailability, and toxicity studies were completed for the IND package, which recently received clearance from the FDA. A first-in-human clinical trial to assess the safety of (*R*)-VK4-116 in healthy individuals is planned for later this year.

Disclosures: Y. Lin: None. **C. Wu:** None. **S. Mounaud:** None. **M. Congdon:** None. **R. Nandre:** None. **B. Ding:** None. **J. Huang:** None. **H. Jin:** None. **P. Terse:** None. **K. Shen:** None. **G. Tawa:** None. **P. Sanderson:** None. **M. De Santis:** None. **D. Lo:** None. **E. Ottinger:** None. **A.H. Newman:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.02/KK2

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA Grant AA029674

Title: Modulatory effects of MC-100093 on astrocytic glutamate transporters and attenuation of relapse-like ethanol drinking behavior in alcohol-preferring rats

Authors: *K. BHOWMIK[1], A. ALOTAIBI[1], M. HASAN[1], M. ABOU-GHARBIA[2], W. E. CHILDERS, Jr.[2], Y. SARI[1];
[1]Dept. of Pharmacol. and Exptl. Therapeut., The Univ. of Toledo, Toledo, OH; [2]Temple Univ. Sch. of Pharm., Philadelphia, PA

Abstract: Relapse-like ethanol drinking behavior depends on changes in the glutamate homeostasis in the mesocorticolimbic circuit. Extracellular glutamate regulation involves multiple transporters, mainly glutamate transporter 1 (GLT-1), which primarily removes most of the extracellular glutamate; and cystine/glutamate antiporter (xCT) is co-localized with GLT-1 to be involved in this mechanism of maintaining glutamate homeostasis. Recent studies showed that MC-100093 treatment (i.p.), a β-lactam non-antibiotic known to increase GLT-1 and xCT expression, reduced chronic ethanol consumption in male and female alcohol-preferring (P) rats. Therefore, this study examined whether MC-100093 attenuates relapse-like ethanol-drinking behavior and restores ethanol-associated alterations in GLT-1 and xCT expression in the medial prefrontal cortex (mPFC) (Prelimbic, PL; and Infralimbic, IL) and nucleus accumbens (NAc) (core, and shell) during relapse-like ethanol behavior. P rats had access to 15% and 30% ethanol and water for five weeks, followed by a one-week deprivation period. During the last four days of deprivation, animals received MC-100093 (100 mg/kg, i.p.), and treatment continued for three days during ethanol re-exposure. MC-100093-treated rats exhibited lower ethanol intake and preference during re-exposure compared to saline-treated groups, across sexes. MC-100093 also attenuated ethanol-induced downregulation of GLT-1 and xCT expression in the mPFC (PL and IL) and NAc (core, and shell). These results report for the first time the efficacy of GLT-1 modulator, MC-100093, on attenuating relapse-like ethanol drinking behaviors and normalizing glutamate transporter-associated adaptations in reward related brain regions.

Disclosures: K. Bhowmik: None. **A. Alotaibi:** None. **M. Hasan:** None. **M. Abou-Gharbia:** None. **W.E. Childers:** None. **Y. Sari:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.03/KK3

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant AA029674

Title: Pharmacological actions of novel GLT-1 enhancers in the brain and liver of male C57BL/6 mice exposed chronically to hydrocodone

Authors: W. WONG[1], A. MOHAMMED[2], W. E. CHILDERS, Jr.[2], M. ABOU-GHARBIA[2], ***Y. SARI**[3];

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Abstract: Chronic exposure to opioid reduced the expression of astrocytic glutamate transporter 1 (GLT-1) in the mesocorticolimbic brain region and ceftriaxone, a beta-lactam antibiotic, attenuated this effect. Importantly, a novel non-antibiotic beta-lactam, MC-100093, was found effective in attenuating fentanyl and morphine overdose-induced reduction in GLT-1 expression in the nucleus accumbens (NAc) as well as attenuated fentanyl-induced liver inflammation and disruption of liver metabolites. In the present study, two novel synthetic non-antibiotic beta-lactams, MC-100093 and MC-290401, and non-beta-lactam bicyclic, MC-290013, were tested in a mouse model of chronic exposure to hydrocodone with focus on GLT-1 expression as well as the transcriptional regulation of GLT-1. This study reports that MC-100093, MC-290401, and MC-290013 treatment attenuated hydrocodone-induced downregulation of GLT-1 in the NAc. MC-100093, MC-290401, and MC-290013 treatments normalized GLT-1 expression in the NAc, and this effect was associated with upregulation of NFκB in the nuclear fraction and downregulation of the expression of mTOR and IKB-α in the cytoplasmic fraction as well as upregulation of pAkt expression in the NAc. Furthermore, histological and statistical analyses revealed that MC-100093, MC-290401, and MC-290013 treatments attenuated chronic hydrocodone-induced liver inflammation (TNF-α, IL-1β, and IL-6). Finally, these GLT-1 modulators attenuated hydrocodone-induced upregulation of hepatic cystine/glutamate antiporter (xCT) and GLT-1. These findings suggest that these novel synthetic GLT-1 modulators may be considered as potential agents to attenuate hydrocodone-induced alterations in glutamate transporters and associated target proteins in the brain and liver.

Disclosures: W. Wong: None. **A. Mohammed:** None. **W.E. Childers:** None. **M. Abou-Gharbia:** None. **Y. Sari:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.04/KK4

Topic: H.08. Drugs of Abuse and Addiction

Title: ESG 1 60, a Novel Dopamine D3 Receptor-Preferring Partial Agonist, Reduces Opioid Taking and Seeking Without Compromising Opioid Analgesia in Rodents

Authors: *V. GUJAR[1], A. H. NEWMAN[2], Z. XI[3];
[1]Mol. Targets and Medications Discovery Br., Natl. Inst. on Drug Abuse / NIH, Baltimore, MD; [2]NIH, NIDA IRP, Baltimore, MD; [3]Intramural Res. Program, Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Opioid use disorders (OUDs) remain a major public health crisis in the United States. Although medications such as methadone, buprenorphine, and naloxone are available, their

effectiveness in preventing relapse is limited, and long-term agonist therapy carries significant abuse liability. Thus, there is an urgent need for safer, non-opioid pharmacotherapies for OUDs. Previous preclinical studies suggest that highly selective dopamine D3 receptor (D3R) antagonists or partial agonists may have therapeutic potential for substance use disorders. However, these compounds often show limited efficacy in reducing psychostimulant self-administration and typically require high doses (10~30 mg/kg) that may produce undesirable side effects. We recently reported that ESG-1-60, a novel D3R-preferring partial agonist with ~20-fold selectivity for D3R over D2R, is more effective than highly selective (>200-fold) D3R antagonists in reducing cocaine self-administration and reinstatement of drug-seeking behavior. These findings suggest that partial agonism at D3R - and to a lesser extent D2R - may contribute to enhanced therapeutic effects. In the present study, we evaluated whether cariprazine and ESG-1-60 similarly reduce opioid-taking and opioid-seeking behaviors. Systemic administration of cariprazine or ESG-1-60 (1-3 mg/kg, i.p.) dose-dependently reduced heroin self-administration and inhibited heroin-primed reinstatement of drug-seeking behavior in rats. Importantly, these doses did not diminish opioid-induced analgesia in the hot-plate test. Fiber photometry using the GRAB-DA sensor revealed that both drugs produced a slow-onset, sustained increase in dopamine release in the nucleus accumbens. This elevation in dopamine may help normalize reward deficits observed in chronic opioid users and reduce opioid craving. Together, these findings demonstrate that moderate D3-preferring partial agonists reduce opioid-taking and opioid-seeking behaviors while preserving opioid analgesia. These compounds therefore represent promising candidates for the development of safer, non-opioid pharmacotherapies for OUDs.

Disclosures: V. Gujar: None. **A.H. Newman:** None. **Z. Xi:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.05/KK5

Topic: H.08. Drugs of Abuse and Addiction

Support: Estonian Research Council grant PRG1473

Title: TETi76 inhibits delta-9-tetrahydrocannabinol (THC)-induced increases in TET enzyme activity in human PBMCs

Authors: *K. PULK, K. ANIER, A. KALDA;
Univ. of Tartu, Tartu, Estonia

Abstract: Drug addiction represents a major global health problem, and effective pharmacological treatments remain limited, highlighting the need to identify novel therapeutic targets. Epigenetic modifications, including DNA methylation and demethylation, play a key role in regulating gene expression and may underlie long-term neuroadaptations associated with drug

addiction. DNA methylation is carried out by DNMT enzymes and is generally associated with the repression of gene expression. The opposite process, DNA demethylation, is mediated by TET enzymes. Studies have shown that long-term cannabis use affects epigenetic mechanisms. Our previous work using human peripheral blood mononuclear cells (PBMCs) showed that repeated *in vitro* exposure to high concentrations (200 ng/ml) of delta-9-tetrahydrocannabinol (THC, the primary psychoactive component of cannabis) resulted in decreased enzymatic activity of DNMT enzymes and increased activity of TET enzymes (Pulk et al., 2025). In addition, the proportion of hydroxymethylated regions across the genome increased, suggesting that high THC concentrations induce widespread DNA demethylation. This may disrupt the regulation of addiction-related genes, indicating that strategies aimed at restoring normal epigenetic patterns could represent a novel therapeutic approach. Although no TET inhibitors are currently available as therapeutic agents, several compounds, including Bobcat339 and TETi76, are available for research purposes and were evaluated in our experiments. To evaluate the efficacy of the TET inhibitors Bobcat339 and TETi76, we performed *in vitro* experiments using PBMCs (n = 6) isolated from the whole blood of healthy male volunteers (27-40 years). We assessed the concentration-dependent inhibitory effects of these compounds on TET enzymes gene expression, enzymatic activity, and cell viability. In this study, we aimed to identify a functional TET inhibitor in the PBMCs model and to investigate whether a suitable TET inhibitor can reverse the THC-induced increase in TET enzyme activity. We found that TETi76 is an effective TET inhibitor in an *in vitro* PBMCs model. We determined that the maximum concentration capable of inhibiting TET enzyme activity was 10 μM. Subsequent experiments using this concentration confirmed that TETi76 can reverse THC-induced changes in our model. These findings provide a foundation for future studies evaluating the efficacy of TETi76 on epigenetic DNA modifiers in the nervous system and *in vivo* models.

Disclosures: K. Pulk: None. **K. Anier:** None. **A. Kalda:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.06/KK6

Topic: H.08. Drugs of Abuse and Addiction

Support: Agencia Estatal de Investigación (AEI), Spain, Project PID2022-137541OB-I00
Plan Nacional sobre Drogas (2024I057)

Title: The psychedelic phenethylamine 25C-NBF, a potent 5-HT2A/2C agonist, reduces cocaine cue reactivity and facilitates extinction of cocaine-associated reward memory in mice.

Authors: B. FUMÀS, P. KLUSKA, A. MELCHOR, J. CAMARASA, E. ESCUBEDO, N. NADAL-GRATACOS, ***R. LÓPEZ-ARNAU**;
Univ. of Barcelona, Barcelona, Spain

Abstract: Cocaine use disorder (CUD) remains a major public health challenge for which effective pharmacological treatments are still lacking. Emerging evidence suggests that psychedelic-assisted interventions may reduce substance use and improve clinical outcomes across several substance use disorders (SUDs). Among these compounds, 25C-NBF (4-chloro-N-[(2-fluorophenyl)methyl]-2,5-dimethoxybenzeneethanamine), a psychedelic phenethylamine analogue of the 2C-X series, acts as a potent 5-HT2A/2C receptor agonist, lacks rewarding and reinforcing properties in preclinical models, and promotes cortical neuroplasticity. Given the critical role of maladaptive neuroplasticity in addiction, compounds that enhance neuronal plasticity may represent novel therapeutic approaches for CUD. Therefore, this study evaluated the effects of 25C-NBF on cocaine-induced behavioral adaptations in mice. Cocaine locomotor sensitization and conditioned place preference (CPP) were established using repeated cocaine administration in Swiss CD-1 male mice. Following a withdrawal period, mice received a single administration of 25C-NBF (10 mg/kg, i.p.) before assessment of cocaine-induced locomotor responses. In a separate cohort, the effects of 25C-NBF on the extinction of cocaine-induced CPP were also evaluated. Following cocaine-induced locomotor sensitization, a single administration of 25C-NBF significantly attenuated both the conditioned locomotor response elicited by the cocaine-associated context (saline challenge) and the locomotor activation induced by a subsequent cocaine challenge. In addition, preliminary results demonstrated that 25C-NBF facilitated the extinction of cocaine-induced CPP, as evidenced by a reduced number of extinction sessions required to abolish cocaine-associated preference. Together, these findings suggest that 25C-NBF reduces the behavioral impact of cocaine-associated contextual cues and facilitates the extinction of cocaine-related reward memories, processes critically involved in relapse vulnerability. Therefore, 25C-NBF scaffold may represent a promising therapeutic strategy for reducing the persistence and influence of cocaine-associated memories in CUD. Further studies are warranted to characterize the effects of 25C-NBF on cocaine reinforcement, including potential sex-dependent effects and underlying neurobiological mechanisms.

Disclosures: B. Fumàs: None. **P. Kluska:** None. **A. Melchor:** None. **J. Camarasa:** None. **E. Escubedo:** None. **N. Nadal-Gratacos:** None. **R. López-Arnau:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.07/KK7

Topic: H.08. Drugs of Abuse and Addiction

Title: Semaglutide Demonstrated Differentiated Efficacies on Preclinical Models of Alcohol and Substance Use Disorders in Rats

Authors: *Z. DING, L. WANG, J. TAN;
WuXi AppTec, Qidong, China

Abstract: Glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as potential modulators of the substance use disorders. However, the effects of semaglutide on distinct classes of abused substances remains incompletely characterized. This study aims to systematically evaluate the effects of semaglutide on preclinical models of alcohol and cocaine use disorders in rats. After an 8-week intermittent access to two-bottle choice (IA2BC) of alcohol drinking training, the 24-hour alcohol intake and alcohol preference of the rats were significantly increased compared to that of the beginning. Compared to vehicle treatment, single dosing of both 0.02 mg/kg and 0.04 mg/kg semaglutide significantly reduced the 24-hour alcohol intake and alcohol preference of the rats. In addition, the total fluid intake exhibited no significant difference between vehicle and 0.02 mg/kg semaglutide treated group, indicating a specific suppression of alcohol intake by semaglutide. In the conditioned place preference (CPP) paradigm, compared to vehicle treatment, single dosing of 0.03 mg/kg semaglutide 1-hour before the post-test significantly suppressed the cocaine CPP expression of rats after an 8-day cocaine conditioning. And compared to previous vehicle treatment, previous semaglutide treatment showed more robust effect on the extinction of cocaine CPP in rats. However, prime with cocaine after extinction significantly reinstated the cocaine CPP in both groups similarly. On the other hand, chronic treatment with 0.03 mg/kg semaglutide once daily for 3 days didn't significantly affect cocaine CPP expression. Nonetheless, compared to previous vehicle treatment, previous semaglutide treatment showed more robust effect on the extinction of cocaine CPP, although not statistically significant. And prime with cocaine after extinction induced a weaker yet without statistically significant reinstatement of the cocaine CPP with previous chronic semaglutide treatment, compared to that with previous vehicle treatment. These findings demonstrated that acute administration of semaglutide could effectively suppress the 24-hour alcohol intake and alcohol preference in rats. Similarly, acute administration of semaglutide significantly suppressed the expression and extinction, but not reinstatement, of cocaine CPP in rats. Our ongoing investigation regarding semaglutide in regulating cocaine induced self-administration in rats will provide further evidence for the role of semaglutide in substance use disorders. Taken together, these preclinical data support semaglutide as potential therapeutics for substance use disorders, especially alcohol use disorder.

Disclosures: Z. Ding: A. Employment/Salary (full or part-time):; WuXi AppTec Co., Ltd. **L. Wang:** A. Employment/Salary (full or part-time):; WuXi AppTec Co., Ltd. **J. Tan:** A. Employment/Salary (full or part-time):; WuXi AppTec Co., Ltd..

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.08/KK8

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA Grant AA029674

Title: Modulatory Effects of MC-290401 on Ethanol Consumption in Female and Male Alcohol Preferring Rats

Authors: *A. ALOTAIBI[1], K. BHOWMIK[1], A. MOHAMMED[2], M. ABOU-GHARBIA[2], W. E. CHILDERS, Jr.[2], Y. SARI[1];
[1]Univ. of Toledo, Toledo, OH; [2]Temple Univ., Philadelphia, PA

Abstract: The role of glutamate transporters has been investigated in models of drug dependence. Extensive studies have demonstrated that ethanol consumption can disrupt glutamate homeostasis within brain reward regions, including the nucleus accumbens (NAc). The disruptive effects of ethanol on glutamate homeostasis are mediated in part through downregulation of glutamate transporter 1 (GLT-1) as well as cystine/glutamate exchanger (xCT). The novel beta-lactam GLT-1 modulator MC-100093 has been shown to reduce ethanol consumption by upregulating GLT-1 and xCT in the NAc. Our laboratory has also identified another GLT-1 modulator, MC-290401. Therefore, we investigated the effects of MC-290401 on ethanol consumption as well as on the expression of GLT-1 and xCT in the NAc. Male and female alcohol-preferring (P) rats were treated with MC-290401 (100 mg/kg/day, i.p.) or saline (i.p.) for five consecutive days following five weeks of free choice of ethanol (15% and 30%) and water. Treatment with MC-290401 significantly reduced ethanol intake in both male and female P rats. Further studies are underway to determine the effect of MC-290401 on GLT-1 and xCT expression in the NAc. These findings suggest that MC-290401 may have the potential to reduce ethanol intake in animals.

Disclosures: A. Alotaibi: None. **K. Bhowmik:** None. **A. Mohammed:** None. **M. Abou-Gharbia:** None. **W.E. Childers:** None. **Y. Sari:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.09/KK9

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA IRP DA000069

Title: (S)-ketamine engages the cingulate cortex to alleviate withdrawal in morphine-dependent rats

Authors: *A. E. TISCHER, Z. J. FRANGOS, O. SOLÍS CASTREJÓN, I. SCHOENBORN, W. DUNNE, J. L. GOMEZ, G. TANDA, M. MICHAELIDES;
Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Relapse in opioid use disorder can be driven by the aversive physical and negative affective symptoms of withdrawal. Ketamine has emerged with clinical potential for alleviating opioid withdrawal, but its underlying mechanisms remain unclear. We hypothesized that (S)-

ketamine, the more pharmacologically active enantiomer, alleviates withdrawal in a rat model of morphine dependence by modulating dopaminergic and opioidergic signaling. Male and female Sprague Dawley rats were continuously exposed to escalating morphine doses (1.6-25.6 mg/kg days 1-10) via subcutaneously implanted osmotic minipumps. On day ten, rats were pre-treated with (S)-ketamine (10 mg/kg i.p.) or saline ten min before undergoing naloxone-precipitated (1 mg/kg i.p.) withdrawal. (S)-ketamine alleviated somatic withdrawal by reducing abdominal spasms, diarrhea, fecal deposits, and ptosis. In a conditioned place aversion paradigm, (S)-ketamine prevented the development of aversion to the naloxone-paired (0.3 mg/kg i.p.) chamber, indicating attenuation of morphine withdrawal-associated negative affect. Next, we used [^{18}F]FDOPA and [^{18}F]FDG PET to examine whether (S)-ketamine rescues changes in dopamine synthesis and brain metabolic activity. (S)-ketamine increased [^{18}F]FDOPA uptake in the nucleus accumbens of morphine-dependent rats compared to controls. This effect was absent following naloxone administration, suggesting opioid receptor signaling contributes to (S)-ketamine-induced increases in dopamine synthesis. Voxel-wise comparisons of [^{18}F]FDG uptake revealed naloxone-induced reductions in cingulate cortex activity of morphine-dependent rats which was rescued by (S)-ketamine pretreatment. Using [^{3}H]DAMGO and [^{35}S]GTPγS autoradiography, morphine dependence did not change MOR density but reduced basal G-protein activity and altered agonist-stimulated G-protein activation in the cingulate cortex, indicating functional adaptations in MOR signaling independent of receptor density. To investigate whether (S)-ketamine modulates opioidergic signaling in the cingulate cortex in vivo, we used genetically-encoded biosensors and fiber photometry to monitor neuronal calcium activity (rGECO) and endogenous opioid peptide neurotransmission (μMass). Preliminary findings show (S)-ketamine enhanced both calcium activity and endogenous opioid peptide neurotransmission during naloxone-precipitated withdrawal. Ongoing studies are using chemogenetics to determine whether activation of cingulate cortex neurons is sufficient to recapitulate (S)-ketamine's behavioral effects on withdrawal.

Disclosures: A.E. Tischer: None. **Z.J. Frangos:** None. **O. Solís Castrejón:** None. **I. Schoenborn:** None. **W. Dunne:** None. **J.L. Gomez:** None. **G. Tanda:** None. **M. Michaelides:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.10/KK10

Topic: H.08. Drugs of Abuse and Addiction

Title: Triple incretin agonist retatrutide reduces alcohol reward, consumption, and relapse-like drinking in rodents

Authors: *A. LOFTÉN[1,2], C. EDVARDSSON[3], S. ALFREJI[4], C. ARANÄS[4], S. WITLEY[4], T. ARCEBISPO EMOUS[4], E. JERLHAG[4];
[1]Dept. of Pharmacology, Inst. of Neurosci. and Physiology, Univ. of Gothenburg / S,

Gothenburg, Sweden; [2]Dept. of Psychiatry for Affective Disorders, Sahlgrenska Univ. Hosp., Gothenburg, Sweden; [4]Pharmacol., [3]Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Alcohol use disorder (AUD) is a major contributor to global morbidity and mortality. Despite its substantial public health burden, only a limited number of pharmacological treatments are available, highlighting the need for novel therapeutic approaches. Targeting the gut-brain axis has emerged as a promising strategy for AUD treatment, with glucagon-like peptide-1 (GLP-1) receptor agonists showing encouraging clinical effects in early studies. In the present study, we investigated the effect of retatrutide, a long-acting unimolecular triple agonist of the GLP-1, glucose-dependent insulinotropic polypeptide, and glucagon receptors. Alcohol reward was assessed in male mice using locomotor activity, conditioned place preference (CPP), and in vivo microdialysis to measure dopamine release in the nucleus accumbens. Voluntary alcohol consumption was evaluated using the intermittent access two-bottle choice paradigm, while relapse-like drinking was assessed using the alcohol deprivation effect paradigm in both male and female rats. Retatrutide attenuated the rewarding properties of alcohol, as demonstrated by reduced alcohol-induced locomotor stimulation, diminished alcohol-induced CPP, and blockade of alcohol-induced dopamine release within the nucleus accumbens in male mice. Notably, retatrutide alone did not affect these measures. Furthermore, acute retatrutide administration significantly reduced voluntary alcohol consumption and prevented relapse-like drinking following alcohol deprivation in both male and female rats, accompanied by reduced food intake and body weight, suggesting additional effects on ingestive behavior. Together, these findings identify retatrutide as a promising candidate for the pharmacological treatment of AUD and support further evaluation in clinical settings.

Disclosures: A. Loftén: None. **C. Edvardsson:** None. **S. Alfreji:** None. **C. Aranäs:** None. **S. Witley:** None. **T. Arcebispo Emous:** None. **E. Jerlhag:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.11/Web Only

Topic: H.08. Drugs of Abuse and Addiction

Support: 1R03DA059714-01

Title: Development of PET radiotracer targeting the orexin 1 receptor

Authors: *I. TOMASSOLI;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Addiction isa chronic relapsing disorder characterized by compulsive drug-seeking which persistsdespite adverse consequences. In recent years, misuse of opioids, bothprescribed and illicit, has increased considerably. The potential involvementof the OX1R system in substance use disorder (SUD) and the lack of PET probestargeting OX1R encouraged us to

develop OX1R imaging probes for PET imaging.The proposedstudy focuses on developing PET radiotracers targeting the orexin 1 receptor. JNJ-54717793is a recent brain penetrant and selective OX1R antagonist with a hOX1 (pki) = 7.83.Our strategy is to use JNJ-54717793 as a starting point since it has shown goodselectivity and affinity for OX1R. As an initial approach, we successfully11C-methylated the amino group in position 7 of JNJ-54717793 (compound **1**).Unlabeled compound **1** was tested in vitro to determine its affinity and selectivityfor the orexin receptor. Then, the blood-brain barrier entry and clearance ofthe newly labeled compound were assessed in rats. A total of 6 animals (3 malesand 3 females) were injected with [11C]**1** and euthanized at 2, 30, and 60min post-injection. Tissues including brain, liver, kidneys, spleen, heart, andblood were collected, and the percentage of injected dose per gram of tissue (%ID/g) was calculated based on tissue weights and gamma counting measurements.The [11C]**1**demonstrated a low micromolar affinity for the OX1R while exhibiting50-fold higher selectivity over OX2R. In addition, the compound showed modestbrain uptake while presenting favorable clearance properties.Overall, ourfindings suggest that this novel radioligand constitutes an encouraging lead candidateto develop PET radiotracers targeting OX1R.

Disclosures: I. Tomassoli: None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.12/KK11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant P60 AA006420
David C. Fairchild Endowed Fellowship

Title: Effects of the GLP-1R, GIPR, and GCGR Triple Agonist Retatrutide on Alcohol and Food Intake in Mice

Authors: *Z. E. KAEGI, P. A. YOUNG, P. C. BENSING, K. TRINH, B. RAMIREZ, S. SINGH, D. CECENA, I. BANAIE, M. KRISHNAN, E. P. ZORRILLA;
Scripps Res., La Jolla, CA

Abstract: Alcohol use disorder (AUD) is a complex psychiatric disorder with underutilized and inadequately effective treatments. Recent studies have implicated the glucagon-like peptide-1 receptor (GLP-1R) in modulating alcohol intake because GLP-1R agonists like exendin-4 and longer half-life semaglutide and tirzepatide can reduce alcohol intake in rodent models of drinking. Here, we test the hypothesis that repeated treatment with retatrutide acetate - a triple GLP-1R, glucose-dependent insulinotropic polypeptide receptor (GIPR), and glucagon receptor (GCGR) agonist acylated with an albumin-binding diacid - reduces alcohol and food intake. Adult male and female mice (C57BL/6J genetic background) received escalating doses of retatrutide (s.c., 2.5, 5, and 10 nmol/kg) or vehicle every other day for 3.5 weeks in a two-bottle

choice (2BC) paradigm to measure voluntary alcohol and water intake with *ad libitum* standard chow. Mice were matched by age and weight into one of three drinking conditions: continuous water, continuous ethanol (20% *v/v*), or intermittent access to ethanol (IAE; MWF 24h per day). Mice received the drinking paradigm for one week before starting treatment. Body composition was collected pre-treatment and again on the day of sacrifice using EchoMRI to determine % fat and lean mass. Data from the first cohort (n = 32, 16 female, 16 male) show that retatrutide significantly reduced body weight (-16.8% ± 1.2 vs. -4.4% ± 0.8 vehicle), fat mass (-27.5% ± 4.6 vs. 1.2 % ± 3.0 vehicle), and lean mass (-15.2% ± 1.1 vs. -4.9% ± 0.9 vehicle). Retatrutide-treated males exhibited incremental reductions in body weight that were greatest after the first 2.5 nmol/kg injection and less extreme thereafter. Retatrutide-treated females exhibited mild rebounds in body weight each week but would decrease following the first injection of each dose. Similarly, water and chow intake across both sexes decreased after the first injections of 2.5 and 5 nmol/kg retatrutide and gradually recovered; by 10 nmol/kg, there was no significant reduction in water or chow intake compared to vehicle animals. In contrast, retatrutide decreased ethanol intake and sustained this effect through all doses in continuous and IAE mice except IAE females, which did not show reliably decreased ethanol intake across any dose. Taken together, these results support the hypothesis that emerging triple agonist GLP-1R/GIP/glucagon compounds reduce alcohol intake and may have therapeutic potential in AUD.

Disclosures: Z.E. Kaegi: None. **P.A. Young:** None. **P.C. Bensing:** None. **K. Trinh:** None. **B. Ramirez:** None. **S. Singh:** None. **D. Cecena:** None. **I. Banaie:** None. **M. Krishnan:** None. **E.P. Zorrilla:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.13/KK12

Topic: H.08. Drugs of Abuse and Addiction

Title: Opioid Receptor Pharmacology and Subjective Effects of Kratom-Derived Compounds

Authors: *E. ZOLALI[1], J. ZUARTH GONZALEZ[1], S. MUKHOPADHYAY[3], C. R. MCCURDY[4], L. R. MCMAHON[1], J. WILKERSON[5], S. OBENG[2];
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Abstract: Kratom, derived from leaves of Mitragyna speciosa, contains more than 40 alkaloids, and mitragynine is the primary active compound. These compounds act as stimulants in low doses, and since they can bind to opioid receptors, they can produce opioid-like effects at high doses. Kratom alkaloids are being used as self-treatment for chronic pain, depression, anxiety, and opioid use disorder. Despite its therapeutic effects, the growing use of kratom has raised concerns regarding the safety of these compounds. In this study, we investigated the receptor

pharmacology of kratom compounds to address the potential risk associated with its bioactive alkaloids. The binding affinities of compounds at human δ-opioid (hDOR), κ-opioid (hKOR), and μ-opioid (hMOR) receptors were determined by radioligand binding assays. [3H] DADLE, [3H] U69,593, and [3H] DAMGO were used to label the hDOR, hKOR, and hMOR, respectively. Functional activity was assessed using HitHunter cAMP assays to quantify receptor-mediated inhibition of cAMP accumulation. We used the drug discrimination procedure to investigate the substitution for morphine. Female (N=4) and male (N=4) Sprague Dawley rats were trained to discriminate 3.2 mg/kg morphine. All compounds were administered 15 minutes before sessions, and percent drug lever responding and response rates were determined on test days. Among the compounds that had sub-micromolar affinity for opioid receptors, all showed selectivity for the MOR over the DOR and KOR, except for Mitragynine pseudoindoxyl, which was more selective for the MOR (Ki = 3.27 ± 0.50 nM) and DOR (Ki = 4.90 ± 0.420 nM) over the KOR (Ki = 56.0 ± 6.26 nM). In the functional assay, all compounds acted as full agonists at DOR. At MOR, speciociliatine was a partial agonist, whereas all the other compounds were full agonists. Mitragynine pseudoindoxyl was the most potent compound at DOR (EC50 = 1.59 ± 0.189 nM) and MOR (EC50 = 3.58 ± 0.766 nM). In vivo, all compounds produced dose-dependent increases in morphine-appropriate responding, except for speciociliatine, speciogynine, and paynantheine. The most potent compounds in producing morphine-appropriate responding were 7-hydroxymitragynine (ED50 = 0.166 mg/kg) and Analog 3 (ED50 = 0.323 mg/kg). All compounds were tested up to doses that decreased response rates. These findings demonstrate differences in the opioid pharmacology of the kratom alkaloids, highlighting the importance of pharmacologically characterizing individual alkaloids to guide the development of safer novel therapeutics and inform policymakers.

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Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.14/KK13

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH NIDA R01 DA059985

Title: Novel desformylflustrabromine-derived α4β2 nicotinic receptor positive allosteric modulators: Brain exposure and efficacy in nicotine self-administration and withdrawal

Authors: A. PALAMAR[1], K. LAUMANN[2], S. JAGWANI[3], Z. XU[3], Z. LI[3], S. SETH[3], H. BEAUZILE[3], J. SHEN[3], A. K. HAMOUDA[4], G. THAKUR[3], M. DAMAJ[1], *C. D. FOWLER[2]; [1]Virginia Commonwealth Univ., Richmond, VA; [2]Univ. of California, Irvine, Irvine, CA; [3]Northeastern Univ., Boston, MA; [4]Pharmaceut. Sci. and Hlth. Outcomes, Univ. of Texas at Tyler, Tyler, TX

Abstract: These studies sought to validate whether novel desformylflustrabromine-derived α4β2 nicotinic receptor positive allosteric modulators (PAMs) mitigate behaviors associated with nicotine addiction in a preclinical mouse model. We first conducted in vitro ADME profiling of two lead compounds, GAT1712 and GAT1728, followed by in vivo pharmacokinetic characterization of GAT1728. Following a single intravenous (tail vein) dose of 9 mg/kg in C57BL/6 mice, GAT1728 reached Cmax of 2,283 ng/mL at 0.25 h, with a terminal elimination half-life of 4.48 h, mean residence time of 3.82 h, and a volume of distribution at steady state of 5.92 L/kg — indicating moderate systemic elimination and extensive tissue distribution. Brain tissue concentrations of GAT1728 were detectable as early as 0.25 h, with high initial levels of 2,302-3,289 ng/g, indicating rapid distribution into the CNS. The brain-to-plasma ratio (Kp) demonstrated rapid initial brain uptake and prolonged brain retention relative to plasma in the terminal phase, important for the compound's therapeutic potential in the CNS. Next, mice were assessed for the effects of GAT1728 and GAT1712 in intravenous nicotine self-administration, the gold-standard translationally relevant model to test the potential efficacy of a drug compound on the drive to consume nicotine. Pretreatment with either GAT1728 or GAT1712 decreased nicotine intake in a dose-dependent manner. As an experimental control, we next examined the effects of the compounds on lever responding for food reward. Pretreatment with GAT1728 or GAT1712 did not significantly alter the number of food pellets earned, demonstrating selective efficacy in modulating nicotine reinforcement. Finally, we examined the effects of GAT1712 on withdrawal behaviors following chronic nicotine exposure. GAT1712 fully reversed the somatic and affective signs of withdrawal in nicotine-dependent mice. Taken together, these findings validate α4β2 nicotinic receptor PAMs as potential therapeutics for nicotine and tobacco cessation.

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Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.15/KK14

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA R01 DA059985

Title: Novel desformylflustrabromine-derived α4β2 nicotinic receptor positive allosteric modulators: Structure-activity relationships, computational binding-Site identification, and in vitro pharmacological characterization

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Abstract: Desformylflustrabromine (dFBr) is a promising scaffold for positive allosteric modulation of α4β2 nicotinic acetylcholine receptors (nAChRs), yet the structural determinants governing its activity across the high-sensitivity (HS; $(\alpha4)_2(\beta2)_3$) and low-sensitivity (LS; $(\alpha4)_3(\beta2)_2$) stoichiometries remain poorly understood. We report a stoichiometry-informed medicinal chemistry campaign exploring systematic modifications of the indole core, C2 prenyl, and ethylamine regions. Two-electrode voltage-clamp (TEVC) recordings in *Xenopus laevis* oocytes identified lead compounds GAT1712, GAT1723, GAT1728, and GAT1739, with rank-order potentiation: GAT1728 = GAT1739 > GAT1723 > GAT1712 > dFBr. Lead compounds did not evoke current in the absence of ACh and did not displace [^{3}H]epibatidine, confirming an allosteric, non-orthosteric mechanism. Among di-halogenated derivatives, 5,6-dihalogenated analogs (GAT1728, GAT1739) produced the greatest potentiation at both stoichiometries, identifying dual halogen substitution at the 5- and 6-positions of the indole ring as the most favorable substitution pattern for α4β2 PAM activity. Computational docking using HS and LS cryo-EM structures (PDB: 6CNJ, 6CNK) identified four candidate transmembrane interfaces. Subsequent 100 ns molecular dynamics simulations on the higher-resolution ACh-bound structures (PDB: 8SSZ, 8ST2) identified the β(+):α(-) transmembrane interface as the productive binding site, where the C5/C6 halogens engage V236 and L237 backbone carbonyls in a halogen-bonding geometry that provides a direct structural rationale for the 5,6-dihalogen SAR, with the indole core anchored by π-stacking against the conserved α(-)Y240. In vitro developability profiling supported GAT1728 as the lead: moderate microsomal stability ($t_{½} \approx 26$ min), favorable LogD (1.8-2.2 in PBS), no hERG inhibition at 1 μM, and high plasma protein binding (85-97% human; 68-85% mouse). Together, these findings define a mechanistically grounded, developable α4β2 PAM lead and establish a structural framework for next-generation stoichiometry-tunable analog design.

Disclosures: K.S. Abdelwahed: None. **S. Seth:** None. **H. Beauzile:** None. **J. Gaona:** None. **E. Phelps:** None. **J. Oman:** None. **N. Pinheiro Menegasso:** None. **P. Gadekar:** None. **S. Jagwani:** None. **Z. Xu:** None. **Z. Li:** None. **R. Kissell:** None. **L. Plant:** None. **M. Damaj:** None. **C.D. Fowler:** None. **J. Shen:** None. **G. Thakur:** None. **A.K. Hamouda:** None.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.16/KK15

Topic: H.08. Drugs of Abuse and Addiction

Support: Samata Therapeutics

Title: Towards safe and effective treatment of substance use disorders: glucose dendrimer-noribogaine eliminates toxicity while preserving therapeutic activity

Authors: *S. B. SHUMWAY[1], D. CHERUKARAVEEDU[1], N. R. KALE[2], J. S. MUMM[1], S. KANNAN[3], R. KANNAN[1], K. PARIKH[1];
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Abstract: =Noribogaine, the active metabolite of ibogaine, has shown therapeutic potential for substance use disorders (SUD) but clinical use is limited by cardiotoxicity, including QT prolongation and fatal arrhythmias, and neurotoxicity risk. We hypothesized that conjugating noribogaine to a glucose dendrimer (GD) would reduce off-target toxicity while retaining therapeutic efficacy by targeting activated microglia and stressed neurons. We synthesized GD-noribogaine via copper-catalyzed click chemistry and confirmed structure by ^{1}H nuclear magnetic resonance and high performance liquid chromatography (diameter: 5.6 nm; zeta potential: -1.4 mV; drug loading: 9%; purity >98%). Cytotoxicity and neuroprotection were evaluated in differentiated human SH-SY5Y neuroblastoma cells (10-100 μM). N-methyl-D-aspartate (NMDA) receptor activity was measured via calcium imaging in differentiated murine HT-22 hippocampal cells (200 nM). Dendritic spine density indicated neuronal connectivity. Vehicle was used as control; experiments were repeated across batches. Cell-based assays were not masked. For cardiotoxicity, we exposed 7-8 days post-fertilization wild-type zebrafish to vehicle, noribogaine, or GD-noribogaine via immersion (n=8/group; 800 μM drug-equivalent; 1 hour) or caudal vein injection (n=6/group) and measured heart rate at 15 and 30 minutes using automated video analysis. Data were analyzed using one-way ANOVA. Free noribogaine demonstrated concentration-dependent toxicity in SH-SY5Y cells with modest reduction in cell viability at 10 μM, pronounced cytotoxicity at 50 μM, and near-complete loss of viability at 100 μM while GD-noribogaine showed minimal effect. In a glutamate (500 μM) excitotoxicity model, GD-noribogaine (10 μM) preserved viability and morphology while free noribogaine partially protected cells but disrupted morphology. Both compounds blocked NMDA-induced calcium influx, confirming GD conjugation does not impair receptor activity. GD-noribogaine preserved protrusion density at healthy control levels while free noribogaine exhibited 8x lower protrusion density ($p<0.05$). In zebrafish, free noribogaine reduced heart rate from 140 to 80 bpm after immersion ($p<0.0001$) and from 180 to 110 bpm at 15 minutes post-injection ($p<0.0001$); GD-noribogaine had no effect via either route. Fluorescence imaging showed GD localization to olfactory bulbs and neuromasts (immersion) and yolk (injection) with no cardiac uptake. This exploratory study suggests GD-noribogaine eliminates cardiotoxicity and neurotoxicity while preserving pharmacological activity, supporting further development for treatment of SUDs.

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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.; Johns Hopkins. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Johns Hopkins. **R. Kannan:** 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.; Johns Hopkins. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Johns Hopkins. **K. Parikh:** 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.; Johns Hopkins. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Johns Hopkins. F. Consulting Fees (e.g., advisory boards); Samata Therapeutics.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.17/KK16

Topic: H.08. Drugs of Abuse and Addiction

Title: 5-MeO-DMT Selectively Attenuates Oral Ethanol Self-Administration in Male and Female Wistar Rats

Authors: *B. RENDA, F. COUTINHO K DUARTE, J. FOLMER, L. MITCHELL, V. J. PHELPS, L. DLUGOSZ, G. A. HIGGINS;
Transpharmation, Fergus, ON, Canada

Abstract: There is emerging evidence in humans that the 5-HT receptor agonist and potent psychedelic, 5-MeO-DMT, could be effective in treating alcohol use disorder (AUD). However, this therapeutic effect has not been reproduced or systematically studied in a preclinical model. The present study aimed to reverse-translate these human findings into a rodent model to determine whether rats exhibit similar reductions in alcohol intake. Using a sucrose fading procedure, male and female Wistar rats (n=16 per sex) were trained to lever press for 4 second access to a liquid reinforcer (0.1 ml) during daily 45-min operant sessions. Rats first responded for 10% sucrose, next the ethanol (EtOH) concentration was increased from 2% to 15%, finally the sucrose concentration was reduced from 10% to 2%. Once stable responding was acquired, the effect of 5-MeO-DMT (0, 0.1, 0.3, 0.6 mg/kg, SC; Pretreatment time: 10 min) on oral self-administration of 15% EtOH with 2% sucrose or 2% sucrose alone was examined. Blood samples were collected from the saphenous vein immediately following completion of EtOH self-administration test sessions to assess blood ethanol concentration (BEC). Both sexes acquired oral EtOH self-administration, achieving pharmacologically relevant BECs (Mean ± SD: males: 0.06 ± 0.03, females: 0.09 ± 0.03). 5-MeO-DMT dose-dependently reduced

responding for EtOH and associated BEC in both sexes. In males, only the highest dose (0.6 mg/kg) reduced active presses (0: 43.25 ± 25.33; 0.6: 24.38 ± 18.83), and both 0.3 and 0.6 reduced BEC (0: 0.06 ± 0.03; 0.3: 0.03 ± 0.02; 0.6: 0.02 ± 0.01) relative to saline (i.e., 0). In females, 0.1 and 0.6 mg/kg reduced active presses (0: 41 ± 17.52; 0.1: 29.47 ± 10.66; 0.6: 24.07 ± 18.37) and all doses reduced BEC (0: 0.09 ± 0.03; 0.1: 0.05 ± 0.03; 0.3: 0.04 ± 0.02; 0.6: 0.03 ± 0.01) relative to saline. Importantly, none of the 5-MeO-DMT doses altered responding for 2% sucrose solution alone [males (0: 95.47 ± 67.61; 0.1: 101.07 ± 57.25; 0.3: 100 ± 49.17; 0.6: 91.93 ± 71.15), females (0: 104.73 ± 59.81, 0.1: 127.12 ± 58.29, 0.3: 133.27 ± 76.70, 0.6: 100.07 ± 52.21)]. 5-MeO-DMT reduced responding for and intake of EtOH in Wistar rats of both sexes without affecting responding for sucrose alone. Doses effective in reducing EtOH intake in rats produce plasma levels comparable to those observed at effective doses in humans. These findings align with recent clinical data and support future investigations into underlying mechanisms and the development of novel 5-MeO-DMT-related therapeutic agents for AUD.

Disclosures: B. Renda: A. Employment/Salary (full or part-time):; Transpharmation. **F. Coutinho K Duarte:** A. Employment/Salary (full or part-time):; Transpharmation. **J. Folmer:** A. Employment/Salary (full or part-time):; Transpharmation. **L. Mitchell:** A. Employment/Salary (full or part-time):; Transpharmation. **V.J. Phelps:** A. Employment/Salary (full or part-time):; Transpharmation. **L. Dlugosz:** A. Employment/Salary (full or part-time):; Transpharmation. **G.A. Higgins:** A. Employment/Salary (full or part-time):; Transpharmation.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.18/KK17

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant NIDA DA050325.

Title: Effect of fentanyl self-administration, abstinence, cue-induced seeking and GLP-1 treatment on continuous heart rate and body temperature regulation in rats.

Authors: *E. G. SHEALY[1], S. BINGAMAN[2], P. S. GRIGSON[3];
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Abstract: Opioid use is a significant public health concern in the United States. Current treatments for opioid use disorder (OUD), while life-saving, also have significant drawbacks such as risk of diversion, risk of withdrawal, and patient burden to access. Recent work in rodent models shows that glucagon-like 1 peptide receptor agonists (GLP-1RAs) rescue the most vulnerable animals during cue-, drug-, and stress-induced opioid seeking. That said, patients with OUD present with tachycardia and body temperature changes. As such, it is important to track both heart rate and body temperature during fentanyl taking and seeking and during rescue

following GLP-1RA treatment. Given that GLP-1RAs provide behavioral protection, we hypothesized that acute treatment with the GLP-1RA semaglutide would mitigate, not only cue-induced fentanyl seeking, but also the high heart rates and low body temperatures seen in rats following long-term exposure to opioids. To test this hypothesis, 12 adult male Sprague-Dawley rats were implanted in the chest cavity with telemetry probes from Data Sciences International (DSI) and heart rate and body temperature were continuously monitored during intravenous fentanyl (n=7) or saline (n=4) self-administration, abstinence, and cue-induced drug seeking. The results showed that, over 14 days of self-administration, some rats self-administered a high number of fentanyl infusions ("high takers"), while others did not ("low takers"). Pre-treatment with the GLP1-RA semaglutide reduced cue-induced seeking and drug-induced reinstatement of fentanyl seeking. During acquisition, 6 h fentanyl self-administration was accompanied by high heart rate and high body temperature relative to saline self-administering controls. During the time off period (i.e., when in the home cage), heart rate was higher for the high takers than for the low takers and heart rate was higher and body temperature lower for the high takers vs. the saline self-administering controls. Finally, semaglutide increased heart rate and decreased body temperature during abstinence and during cue-induced seeking. Overall, results showed individual differences in fentanyl self-administration that were accompanied by individual differences in heart rate and body temperature during the acquisition period and protection from cue-induced seeking by treatment with the GLP-1RA, semaglutide, which also increased heart rate and decreased body temperature. Replication with an additional cohort is underway. This work was supported by NIDA UH3 DA050325.

Disclosures: E.G. Shealy: None. **S. Bingaman:** None. **P.S. Grigson:** F. Consulting Fees (e.g., advisory boards); Eli Lilly.

Poster

PSTR375: Drug Discovery and Novel Therapeutics for Substance Use Disorders

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Program #/Poster #: PSTR375.19/KK18

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01AA032636

Title: Diphenyl-1,2,4-Oxadiazole Analogs as RXFP3 NAMs: Design, Synthesis and SAR studies

Authors: *C. JIN[1], J. HUSSAIN[1], M. RAHMAN[1], D. BARRUS[1], E. A. GAY[1], J. BESHEER[2]; [1]RTI Intl., Research Triangle Park, NC; [2]Univ. of North Carolina - Chapel Hill, Chapel Hill, NC

Abstract: The neuropeptide relaxin-3/RXFP3 system belongs to the relaxin/insulin superfamily and is involved in many important physiological processes, such as stress responses, appetite control, and motivation for reward. Relaxin-3/RXFP3 antagonism is a novel strategy for drug development to treat alcohol use disorder (AUD). We recently discovered the first-in-class

RXFP3 negative allosteric modulators (NAMs) that can dose-dependently block endogenous relaxin-3 agonist activity both in vitro and in vivo. In rat behavioral studies, our compounds significantly attenuated alcohol self-administration without affecting sucrose self-administration and general locomotor activity, demonstrating the potential of RXFP3 NAMs as promising drug candidates for AUD. In order to further improve potency and ADME/PK properties, we have designed and synthesized a series of diphenyl-1,2,4-oxadiazole analogs. We have evaluated these novel compounds in RXFP3 functional assays, assessed their selectivity against RXFP1 and RXFP4, two members of the relaxin/insulin superfamily, and established their ADME/PK profiles. Finally, we have built a full-length model of RXFP3 based on the relaxin-3-RXFP3-$G\alpha_i$ cryo-EM structure (PDB: 9KFI) and revealed that our RXFP3 NAMs bind to RXFP3 in an allosteric intracellular site above where the α5 Ras helix binds. Taken together, these studies will lead to further development of potent and selective NAMs to probe RXFP3 functional antagonism in the brain.

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Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.01/KK19

Topic: I.01. Attention

Support: KAKENHI JP (23K06788)

Title: Movement analysis of behaviors associated with anticipation of reward timing in macaques

Authors: *M. HATSUSHI[1], T. SETOGAWA[1,2], T. IZAWA[1], R. SHINOHARA[1], J. MATSUMOTO[1,2], H. NISHIMARU[1,2];
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Abstract: When animals can predict the timing of reward delivery, they appropriately allocate attention to the expected reward and prepare actions to obtain it. Such timing prediction behaviors have traditionally been assessed using limb movements and pupil diameter. Recently, subtle changes in animals' facial expressions have been proposed as an additional indicator of such goal-directed behaviors. Markerless pose estimation tools, such as DeepLabCut, have enabled the detection and quantification of subtle movements in animals. In the present study, we analyzed arm movements, pupil size, and facial expressions of monkeys during the performance of a reward-based task using DeepLabCut, and examined whether these behavioral changes can be associated with reward-seeking behaviors. Two Japanese macaques were trained on a delayed non-matching to sample (DNMS) task. In this task, after a sample stimulus was presented

repeatedly, a new stimulus was presented as a target (the target phase). Monkeys were required to press a button within 2 s of target onset to obtain a liquid reward. Trials were aborted if the monkey failed to respond correctly during the target phase or pressed the button before the target phase. This DNMS task consisted of random and fixed sessions. In the random session, the number of sample presentations varied from 2 to 4 on a trial-by-trial basis. In contrast, in the fixed session, the number was fixed at 3, allowing the monkeys to predict the timing of target appearance and reward delivery. These two sessions were alternated after a predetermined number of trials. Videos of the monkeys' faces and arms recorded during DNMS task performance were analyzed using DeepLabCut. In these monkeys, preparatory movements of the button-pressing arm were observed before target presentation during the fixed session, but not before sample presentations. In addition, characteristic changes were observed in behavioral signals that were not explicitly required for task performance, including pupil size and uninstructed facial movements. Pupil size gradually increased with each sample presentation and reached its maximum during the target presentation. Furthermore, movements of several facial regions, including the ears, gradually changed as the timing of target presentation drew near. These movements were independent of those associated with reward-related licking behavior. Taken together, these results indicate that behavioral signs associated with timing prediction can be observed not only in task-related arm movements but also in pupil size and facial movements, which may reflect reward expectation.

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Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.02/KK20

Topic: I.01. Attention

Support: R01EY033726
F32EY035963

Title: Anticipatory Processing of Cued Target and Distractor Locations Compete within a Shared Neural Substrate

Authors: *Z. V. REDDING, Y. DING, I. C. FIEBELKORN;
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Abstract: Recent work has revealed behavioral and electrophysiological evidence that top-down attentional control can suppress interference from distractors; however, the underlying neural mechanisms remain unclear. Much of the previous work in humans and non-human primates has focused on suppression occurring after distractor onset (i.e., reactive suppression), with ongoing debate about whether suppression of predictable distractors can occur in anticipation of distractor

onset. Here, macaques were trained to perform a visual target-detection task with cues indicating the upcoming location of a target, a distractor, or both. We simultaneously recorded from the frontal eye fields (FEF) and the lateral intraparietal area (LIP)—two critical nodes of the cortical network responsible for coordinating the deployment of spatial attention—and visual area V4. Increased spike rates were observed in cue-responsive FEF and LIP units during the delay period following presentation of either target or distractor cues, consistent with top-down anticipatory neural activity. On trials containing both cue types, delay-period spike rates were relatively lower, consistent with competition between target- and distractor-related anticipatory processes. Demixed principal component analyses similarly revealed that delay-period population activity carried information about cue location, reflecting the trial-by-trial deployment of location-specific attentional resources (i.e., spatial attention); however, no components distinguished spiking activity following target cues from that following distractor cues. When training a linear classifier on target or distractor cue location, the decoding axis of the first location-specific component reliably predicted the location of either cue type, again consistent with competitive usage of the two cue types. In summary, these findings indicate anticipatory, attention-related processing following both spatially informative target and distractor cues. Such anticipatory processing, however, appears to rely on a shared neural substrate. While analyses of firing rates revealed competition within a shared neural population, analyses of temporal dynamics and cross-regional coupling may reveal key differences in the deployment of anticipatory attentional resources for target versus distractor processing.

Disclosures: Z.V. Redding: None. **Y. Ding:** None. **I.C. Fiebelkorn:** None.

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

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Program #/Poster #: PSTR376.03/KK21

Topic: I.01. Attention

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Title: Attentional selection without recurrent attentional modulation

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Abstract: Your attention is competed for by numerous objects at any given moment. Recurrent attentional modulation of neural activity in sensory cortices supports shifts of attention, enhancing pertinent stimuli and suppressing distracting information. However, feedforward sensory responses alone can be sufficient to select such objects, bringing into question the necessity of recurrent attentional modulation for attentive behavior. We investigated whether recurrent attentional modulation of sensory activity occurs when feedforward activation is sufficient for attentional selection. Ultimately, we sought to determine whether recurrent modulation always follows the deployment of selective attention, even when feedforward selection is sufficient, or whether it is deployed only to support subsequent shifts. We recorded population spiking activity in the mid-level visual cortical area V4 of two macaque monkeys performing a salient-distractor variant of a visual search task, in which recurrent attentional enhancement and distractor suppression are typically potent. In trials where monkeys quickly identified the behavioral target, recurrent attentional modulation was absent. Neither target enhancement nor salient distractor suppression was observed. Attentional modulation was observed in trials where the monkey was slower to identify the target. Deep learning classification confirms that the feedforward response contained information regarding the bottom-up deployment of attentional selection. Interestingly, feedforward attentional selection was associated with latency differences in the visual response to the target versus the salient distractor. These findings suggest that recurrent attentional modulation in the visual cortex is not always deployed with attentional selection, but only to support a shift of attention in the absence of a useful feedforward selection event. This brings into question the commonly held notion of a critical role for recurrent processing in cognition and consciousness.

Disclosures: J.A. Westerberg: None. **P.R. Roelfsema:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Phosphoenix B.V..

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.04/KK22

Topic: I.01. Attention

Support: P50MH132642
RO1 EY017699
R01MH137624

Title: From uncertain cues to attentional states: thalamic contributions to spatial attention in the macaque

Authors: *Y. WU[1], R. BOSHRA[3], B. MOREA[2], C. KISSEL[2], M. RODRIGUEZ[2], S. KASTNER[1];

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Abstract: Adaptive behavior requires the brain to selectively prioritize spatial locations based on often ambiguous sensory evidence. Consider a soccer goalkeeper defending a penalty kick: when pre-kick bodily cues are congruent, the goalkeeper can confidently commit to one side; when cues conflict through feints, attention must be effectively distributed across both sides. This captures a fundamental challenge in attentional control: how does the brain flexibly deploy spatial attention when a directional cue is informative but internally inconsistent? Neurophysiology studies in mice found that the mediodorsal thalamus (MD) tracks uncertainty and amplifies cortical signals when uncertainty is high. Here, we examine how and where the brain interprets perceptual uncertainty to guide dynamic spatial attention. We trained two macaques on an endogenous attention task in which a colored random-dot cloud (400 ms) served as a predictive spatial cue (80% validity) with trial-by-trial variation in color coherence. The dominant color (red or blue) indicated the most likely target location (lower left or lower right quadrant). After a variable delay (0.35-1.4 s), a near-threshold contrast change occurred at the cued location (80%), upper same-hemifield location (10%), or lower opposite-hemifield location (10%); 25% were catch trials. Color coherence was set at three levels based on individual psychometric curves from a saccade discrimination task. Both monkeys showed systematic behavioral effects of cue coherence. At high coherence, detection performance was significantly better at the cued location, reflecting robust endogenous spatial attention. This effect decreased as a function of decreasing cue coherence. Preliminary data from a variant of the Egly-Driver task suggest that MD is also engaged during sustained attentional modulation. We hypothesize that MD represents uncertainty signals that are utilized to coordinate distinct attention states within the thalamocortical network. We will perform simultaneous recordings from the medial pulvinar, MD, lateral intraparietal area, and frontal eye fields during this task to study the dissociated roles of pulvinar and MD in attentional control under perceptual uncertainty.

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Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.05/KK23

Topic: I.01. Attention

Title: A waveform-based cell-type classification framework for the macaque dorsal pulvinar

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[1]Psychology, [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: The primate pulvinar is a higher-order thalamic nucleus that, through its dense reciprocal connections with cortex, plays a key role in regulating visual attention. In cortex, attentional modulation is shaped by interactions among distinct, functionally specialized neuronal populations, which can be separated into putative inhibitory and excitatory classes using extracellular waveform features, where narrow waveforms are often associated with inhibitory interneurons and broad waveforms with excitatory cells. Whether pulvinar cell types are comparably separable by their extracellular waveform characteristics, and how these classes contribute to visual attention, remains unknown. Here, we systematically examined the diversity of waveform features in the pulvinar, as a foundation for relating waveform-defined classes to attentional modulation. We performed dense recordings from the dorsolateral pulvinar of two adult male rhesus macaques using linear probes with 128 channels. These data were collected while animals performed a set of behavioral tasks, including a modified version of the Egly-Driver task, in which an informative spatial cue indicated the location of a target presented at perceptual threshold and with high probability. We sorted spikes using Kilosort4 and curated the output manually. For each well-isolated neuron, we extracted the trough-to-peak duration and repolarization time. We then used these features to classify neurons with a Gaussian mixture model, which identifies clusters directly from the data without imposing arbitrary thresholds, selecting the number of groups by the Bayesian information criterion. Building on this classification, we are testing whether putative inhibitory and excitatory populations, identified by combining the waveform classes with cross-correlogram analysis, are differentially modulated by attention. In our preliminary analysis of 341 neurons, the classification yielded two cleanly separated populations: a narrow-spiking population comprising 22% of our neurons with a short mean trough-to-peak of 0.26 ms (SD = 0.06), and a broad-spiking population comprising 78% with a longer mean trough-to-peak of 0.73 ms (SD = 0.09). This bimodal separation indicates that the pulvinar parallels the narrow- and broad-spiking distinction described in cortex, with comparable proportions. Together, this work confirms that the pulvinar contains distinct waveform-defined classes and lays the groundwork for resolving how distinct thalamic cell types support visual attention.

Disclosures: Y. Shi: None. **R. Boshra:** None. **Y. Wu:** None. **S. Kastner:** None.

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.06/KK24

Topic: I.01. Attention

Support: NIMH Grant R01MH137057

Title: The effect of MK-801 on attentional performance in the rodent continuous performance test (rCPT)

Authors: *K. N. HOFFMANN[1], Y. LI[1], M. ALVES[1], N. PEARSON[1,3], Z. HUSAINI[4,1], K. MARTINOWICH[2,5,6], J. A. MIRANDA-BARRIENTOS[2,6], G. V. CARR[1,4];
[1]Drug Discovery, [2]Lieber Inst. for Brain Develop., Baltimore, MD; [3]Biochem., Grinnell Col., Grinnell, IA; [4]Physiology, Pharmacology, and Therapeut., [5]The Solomon H. Synder Dept. of Neurosci., [6]Psychiatry and Behavioral Sci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Attention deficits are a core feature of neuropsychiatric disorders, such as schizophrenia and attention deficit/hyperactive disorder (ADHD). Sustained attention, the ability to focus on stimuli over time, is a critical cognitive domain that is correlated with patient quality of life and functional outcome. MK-801, a potent NMDA receptor antagonist, is commonly used to model attention deficits and schizophrenia-like behavioral changes. In this study, we sought to produce a comprehensive dose-response profile of acute MK-801 in the rodent continuous performance test (rCPT). The rCPT is a validated translational assay for measuring sustained attention. We investigated the effects of both intraperitoneal (i.p.) and subcutaneous (s.c.) administration of MK-801. Following previous in-house and published studies, we used a time-on-task (TOT) rCPT protocol. The i.p. administration cohort consisted of male and female C57BL/6J mice (n=14 males, 8 females) treated with vehicle (saline), 0.05 mg/kg MK-801, 0.10 mg/kg MK-801, 0.15 mg/kg MK-801, 0.20 mg/kg MK-801, 0.30 mg/kg MK-801 and 0.60 mg/kg MK-801. Treatment was administered 15 minutes prior to TOT probe sessions. Our findings suggested that low doses of MK-801 (0.05-0.15 mg/kg) increased rCPT response rate and overall performance, whereas high doses of MK-801 (0.20-0.60 mg/kg) decreased response rate and performance in the rCPT. Due to differences in drug sensitivity and behavioral structure, all analyses were performed within a sex-specific framework. For the s.c. treatment cohort, 10-week-old male and female C57BL/6J mice (n=16 males, 7 females) were treated with vehicle (saline), 0.10 mg/kg MK-801, 0.20 mg/kg MK-801 and 0.30 mg/kg MK-801. Treatment was administered 30 minutes prior to TOT probe sessions. Testing and analysis is still ongoing. Preliminary EEG recordings on males treated with 0.10 MK-801 mg/kg s.c. (n=8) demonstrated a significant increase in total overall power (unpaired *t*-test, p=0.0002), delta bands (unpaired *t*-test, p=0.0006), theta bands (unpaired *t*-test, p=0.0001) and alpha bands (unpaired *t*-test, p=0.0012). Males treated with 0.30 MK-801 mg/kg i.p. (n=12) also showed a significant increase in total overall power (unpaired *t*-test, p=0.0017), delta bands (unpaired *t*-test, p=0.0008), and theta bands (unpaired *t*-test, p=0.0037). Collectively, these findings establish a comprehensive profile of acute MK-801 administration in the rCPT, which may aid in the development of novel therapeutics for disorders such as schizophrenia and ADHD.

Disclosures: K.N. Hoffmann: None. **Y. Li:** None. **M. Alves:** None. **N. Pearson:** None. **Z. Husaini:** None. **K. Martinowich:** None. **J.A. Miranda-Barrientos:** None. **G.V. Carr:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Own stock options in LongTermGevity, Inc. F. Consulting Fees (e.g., advisory boards); Scientific advisor to LongTermGevity, Inc.

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.07/KK25

Topic: I.01. Attention

Support: NIH R01MH123687

Title: Neuronal communication subspaces emerge during top-down guided attention across the fronto-striatal network and strengthen with learning

Authors: *P. G. POGGI[1], S.-A. HASSANI[1], D. BRUST[1], A. NEUMANN[1], P. H. TIESINGA[2], T. WOMELSDORF[1,3];
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[3]Vanderbilt Brain Inst., Nashville, TN

Abstract: Brief routing states between neurons have been documented in the fronto-striatal network during goal-directed behavior, but how population-level ensembles coordinate to guide endogenous attention and communicate relevant information remains unknown. We addressed these questions by measuring the alignment of neuronal activity across the lateral prefrontal cortex (lPFC), anterior cingulate cortex (ACC), and caudate nucleus (CD) in two non-human primates during self-guided attention in a feature-rule learning task. The task involved freely visually sampling three objects and selecting one by maintaining fixation for 0.7 s. We quantified interareal population alignment around object fixation using canonical correlation analysis (CCA), focusing on the first canonical component. Alignment increased around fixation, defining communication subspaces that predicted object choice across all area pairs. CCA weights showed a majority of lPFC and ACC neurons participated similarly across area-pair subspaces, suggesting shared communication channels. To examine learning-dependent changes, we classified trials as explorative or exploitative using Hidden Markov modeling. The ACC-lPFC subspace was weaker during exploration and significantly strengthened during exploitation; the ACC-CD subspace was strongest during the transition from explorative to exploitative states, and the lPFC-CD subspace was similarly strong across states. Neuronal weight analysis showed that distinct neural ensembles were active in explorative and exploitative states. Complementary decoding analyses showed above-chance decoding of joint object location and expected object value, increasing around fixation onset. These results demonstrate that communication subspaces emerge across the lPFC-ACC-CD network as subjects guide gaze toward behaviorally relevant objects. The learning dependent changes of subspaces across ACC-lPFC and ACC-CD suggest that ACC-centered interactions become increasingly coordinated throughout learning, while stable lPFC-CD alignment may support object selection and value updating. The decodability of the expected value and location of fixated objects from neurons participating in the subspace suggests that alignment of population-level spiking activity could be instrumental for attentional selection during and after learning.

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Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR376.08/KK26

Topic: I.01. Attention

Support: National Institute of Mental Health (NIMH) - R01MH137057

Title: Medial prefrontal cortex (mPFC) - locus coeruleus (LC) projection neurons alter attention related neural population dynamics and norepinephrine release in the rodent continuous performance test (rCPT)

Authors: *J. J. REHG[1], D. OLIVARES[2], S. ADIRAJU[4], K. MARTINOWICH[3], G. V. CARR[5], J. A. MIRANDA-BARRIENTOS[1];
[2]Lieber Inst. for Brain Develop., [1]Lieber Inst. for Brain Develop., Baltimore, MD; [3]Lieber Inst. for Brain Develop., Pasadena, MD; [4]Johns Hopkins Med. Institutions, Baltimore, MD; [5]Drug Discovery, Lieber Inst. For Brain Develop., Baltimore, MD

Abstract: The medial prefrontal cortex (mPFC) serves as a central node in attentional processing by exerting top-down control to allocate cognitive resources toward behaviorally relevant stimuli based on learned context and expectations. mPFC neurons project to multiple cortical and subcortical regions, including the locus coeruleus (LC)—the brain's primary source of norepinephrine (NE). The mPFC furthermore receives reciprocal inputs from the LC, which release NE to modulate mPFC neuronal activity and downstream cellular signaling. We have previously shown enhanced functional connectivity between the mPFC and LC in mice during the rodent continuous performance test (rCPT) (Hallock and Adiraju et al, 2024), a translational sustained attention task, and we recently demonstrated that selective chemogenetic modulation of mPFC neurons projecting to the LC (mPFC-LC projectors) improves attentional performance across multiple task conditions by enhancing discrimination (Rehg et al, 2026). However, some of the cellular and circuit mechanisms by which these neurons exert their effects still remain to be elucidated. Here, we test the hypothesis that activation of mPFC-LC projectors induce NE release in the mPFC, which reorganizes mPFC neuronal dynamics associated with task performance. To test this hypothesis,we performed i) photometry recordings using the NE biosensor GRABNE in mice expressing the excitatory DREADDs in mPFC-LC projectors and ii) performed LFP recordings within the mPFC during rCPT performance after activation of mPFC-LC projectors. We found that mPFC-LC activation drove a significant increase in mPFC NE tone, which correlated with an increase in mPFC LFP power in the delta and theta frequency bands surrounding rCPT responses following the same manipulation. To further examine the cellular mechanisms underlying LFP changes during task performance following mPFC-LC activation, we are currently performing in vivo calcium imaging recordings of mPFC neurons during rCPT while selectively activating mPFC-LC projectors. These experiments will allow us to quantify how this manipulation reshapes neuronal dynamics across distinct mPFC populations and to identify activity patterns associated with anticipatory and post-response phases of task performance.

Disclosures: J.J. Rehg: None. **D. Olivares:** None. **S. Adiraju:** None. **K. Martinowich:** None. **G.V. Carr:** None. **J.A. Miranda-Barrientos:** None.

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR376.09/KK27

Topic: I.01. Attention

Support: 5R01MH137057-03

Title: Sex-dependent effects of target probability and reward magnitude on sustained attention and response strategy in the mouse rCPT

Authors: *Y. LI[1], K. MARTINOWICH[1,2,3], J. A. MIRANDA-BARRIENTOS[1,3], G. V. CARR[1,4];
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Abstract: Attentional control is frequently disrupted in neuropsychiatric disorders, yet translational assays that systematically capture variation in attentional demand, motivation, and response control remain underdeveloped. The rodent continuous performance task (rCPT) provides an important bridge between clinical and preclinical research, but the influence of core task parameters on performance strategy and the time-on-task vigilance decrement is not fully understood. We tested whether target probability and reward magnitude shape rCPT performance and the vigilance decrement in male and female mice across 90-min sessions under three target probabilities (20%, 50%, or 80% S+) and two reward volumes (10 or 20 µl), analyzed across six 15-min bins using mixed-effects models (male n = 8-12; female n = 4-5 per condition). Both parameters regulated performance in distinct but interacting ways: target probability modulated sensitivity in both sexes and response criterion in a sex-dependent pattern (d′: male, $p < 0.001$; female, $p < 0.001$; c: male, $p < 0.001$; female, n.s., $p = 0.064$), with males showing pronounced time-on-task interactions (d′, $p = 0.006$; c, $p < 0.001$; HR, $p < 0.001$; FAR, $p < 0.001$) and females showing stronger context-dependent modulation when probability and reward interacted (d′, $p = 0.029$; FAR, $p = 0.007$). Reward magnitude broadly shifted sensitivity and response bias in both sexes (d′: male, $p < 0.001$; female, $p = 0.004$; c: male, $p < 0.001$; female, $p < 0.001$). Variance partitioning indicated stronger reward-related contributions to behavioral variance in females, suggesting reward sensitivity as a sex-specific modulator of task engagement. Response rate declined across the session ($p < 0.001$), while stimulus orientation remained largely stable, arguing against generalized disengagement. PCA revealed sex-dependent dimensions related to response style, engagement, and attentional stability, with trajectories varying by sex and reward condition. These findings demonstrate that target probability and reward magnitude are potent regulators of rCPT performance and the vigilance decrement, and that systematic modeling of these parameters can sharpen the sensitivity of translational mouse assays for detecting treatment-relevant cognitive phenotypes.

Disclosures: Y. Li: None. **K. Martinowich:** None. **J.A. Miranda-Barrientos:** None. **G.V. Carr:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); G. V. Carr: owns stock options in LongTermGevity, Inc.. F. Consulting Fees (e.g., advisory boards); G. V. Carr: scientific advisor to LongTermGevity, Inc..

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

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Topic: I.01. Attention

Support: NSF Grant 2120539
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Title: Coding of concurrent and internal information in the macaque attention network

Authors: *P. CAVANAH[1,2], Z. V. REDDING[2,1], I. C. FIEBELKORN[2,1];
[2]Neurosci., [1]Univ. of Rochester, Rochester, NY

Abstract: Most everyday visual tasks demand selective processing of both information from the external environment and information from internal memory stores (e.g., information held in working memory). For instance, reading a scientific figure requires both external processing of the figure itself and retention of recently processed visual elements in working memory. Previous electrophysiological investigations of these two processes have yielded alternative accounts of whether distinct neural populations represent behaviorally relevant external versus internal information—ranging from proposals that these populations are dissociable and nonoverlapping, to proposals that a shared circuit bears the load of representing and selecting both external and internal information. An important question for informing these debates is how neural populations adjust to the common, everyday situation of simultaneous external and internal demands. Here, we trained a male cynomolgus macaque to perform a behavioral task with conditions that emphasize processing and selection of (i) external information, (ii) internal information, or (iii) both external and internal information (i.e., dual-task trials). Behavioral results show that there is a cost in accuracy and response times on dual-task trials relative to external-only and internal-only trials. While the macaque performed this behavioral task, we used linear probes to record from four areas—prefrontal cortex (PFC), frontal eye fields (FEF), lateral intraparietal area (LIP), and visual area V4. We first replicated previous findings that higher-order areas (PFC, FEF, and LIP) have more representational overlap than sensory areas (V4). We then examined how representational overlap shifted on dual-task trials, finding, for example, that dual-task trials yielded a higher proportion of neurons that were selective for internal information than internal-only trials. This pattern was observed across all areas (average of 12.6% increase in internal-selective units). These preliminary results support the idea that there is limited representational capacity for concurrent external and internal processing, and that

in multitasking scenarios, neurons can be recruited to expand representational bandwidth. Data collection and analysis are ongoing.

Disclosures: P. Cavanah: None. **Z.V. Redding:** None. **I.C. Fiebelkorn:** None.

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.11/KK29

Topic: I.01. Attention

Support: R01MH137057

Title: Distinct spatial and topographical organization of medial prefrontal cortex-locus coeruleus (mPFC-LC) and ventral tegmental area (mPFC-VTA) projection neurons

Authors: *D. OLIVARES[1], J. REHG[1], H. ALGRAIN[1], S. C. PAGE[3], K. MARTINOWICH[2], G. V. CARR[4], J. A. MIRANDA-BARRIENTOS[1];
[1]Lieber Inst. for Brain Develop., Baltimore, MD; [2]Lieber Inst. for Brain Develop., Pasadena, MD; [4]Drug Discovery, [3]Lieber Inst. For Brain Develop., Baltimore, MD

Abstract: Sustained attention, the ability to maintain task- or goal-oriented focus, is crucial for higher-level cognition, and is frequently impaired in individuals with neuropsychiatric disorders, including attention-deficit/hyperactivity disorder and schizophrenia. While attentional processes recruit a broad network within the brain, the medial prefrontal cortex (mPFC) has emerged as a key node for attentional control. The mPFC sends long-range projections to subcortical regions including the locus coeruleus (LC) and ventral tegmental area (VTA), and we recently showed that chemogenetic activation of mPFC neurons projecting to the LC (mPFC-LC projectors) improves performance in mice during a translational sustained attention task (Rehg et al, 2026). While activation of mPFC-LC projectors engaged LC and peri-LC circuits, tracing analysis of mPFC-LC projectors revealed fibers within the VTA (Rehg et al, 2026), suggesting that some mPFC-LC projectors may also target the VTA. In this study, we anatomically characterized mPFC neurons projecting to the LC and VTA (mPFC-LC and -VTA projectors) and tested whether these populations constitute segregated or overlapping circuits. To this end, we injected retrograde viral vectors encoding tdTomato or GFP into the LC and VTA, respectively, to label projection-defined mPFC neurons and quantify the proportion of mPFC-LC or -VTA projectors across the rostrocaudal axis. Additionally, we used RNAscope with probes targeting laminar markers (Frem3 and Pcp4, for layers 3 and 5 respectively) to determine the laminar distribution of these projection-defined populations. We found that mPFC-LC and -VTA projectors are largely segregated populations, with 33% of labeled neurons being mPFC-LC projectors (GFP+), 48% mPFC-VTA projectors (tdTom+), and 19% mPFC-LC/VTA projectors (GFP+/tdTom+). Notably, mPFC-LC projectors were enriched in rostral regions of the mPFC, whereas mPFC-VTA projectors were more prominent caudally. Consistent with this topographic organization,

we observed spatial segregation across cortical layers, with these populations occupying distinct laminar distributions. In conclusion, our findings demonstrate that mPFC-LC and -VTA projectors form largely segregated circuits with distinct rostrocaudal and laminar organization.

Disclosures: D. Olivares: None. **J. Rehg:** None. **H. AlGrain:** None. **S.C. Page:** None. **K. Martinowich:** None. **G.V. Carr:** None. **J.A. Miranda-Barrientos:** None.

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR376.12/KK30

Topic: I.01. Attention

Support: NIH EY014924
Brain and Behavior Research Foundation

Title: Dual-timescale encoding of attentional engagement in medial frontal cortex predicts primate viewing behavior

Authors: *W. HU[1,2], X. CHEN[3];
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Abstract: In the current digital world, social media is designed to capture and sustain our attention, and the time we choose to spend with what we see has become increasingly consequential. Yet the neural mechanisms that encode attentional engagement remain poorly understood. We recorded from the supplementary eye field (SEF) using high-density Neuropixels probes while two macaques freely explored image arrays in a self-paced free-viewing paradigm.
Behaviorally, viewing duration decomposed into a long-lasting component that changed gradually across the session (proactive engagement) and a short-lasting, image-dependent component that fluctuated from trial to trial (reactive engagement). We inferred proactive engagement from several behavioral measures jointly, and reactive engagement from self-paced viewing time after partitioning out the proactive contribution. SEF neurons encoded both proactive engagement and reactive engagement. Pre-stimulus activity covaried with proactive engagement, manifesting as a graded baseline shift that built gradually rather than as a discrete state change. Stimulus-evoked activity predicted trial-to-trial fluctuations during passive fixation, before free viewing began, and persisted throughout active exploration. The two signals were dissociable at the single-neuron and population levels and were distributed differently across laminar compartments. In Cox proportional-hazards models of disengagement, both pre-stimulus and post-stimulus activity predicted the instantaneous probability that viewing would terminate, and together they improved model performance beyond either signal alone.

These findings reveal two engagement-related signals in medial frontal cortex that operate on distinct timescales: a slow anticipatory signal reflecting sustained attentional state and a faster stimulus-driven signal predicting moment-to-moment viewing behavior. Their laminar organization and complementary contributions to disengagement hazard suggest that SEF coordinates both proactive and reactive components of primate attentional engagement.

Disclosures: W. Hu: None. **X. Chen:** None.

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR376.13/KK31

Topic: I.01. Attention

Support: 1R21MH130066

Title: Molecularly distinct insula subcircuits regulate disparate attentional domains

Authors: *O. FRANK, H. L. HALLOCK;
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Abstract: Attention is a multifaceted cognitive process that includes sustained attention, the ability to maintain focus on relevant stimuli over time. Deficits in sustained attention are associated with numerous neuropsychiatric disorders. Continuous performance tests (CPTs) are widely used to assess sustained attention in both humans and rodents. In rodents, the frontal cortex (FC) contributes to sustained attention, selective attention, and response inhibition, and receives projections from the insular cortex (IC), a region also implicated in attentional control. To examine the role of insula-FC circuitry in attention, we used a dual-virus strategy to express the inhibitory DREADD receptor hM4Di selectively in insula neurons projecting to the FC. Mice received clozapine-N-oxide (CNO) prior to performing the rodent CPT (rCPT) under three conditions: Stage 3 (50% target probability), Probe 1 (20% target probability; increased sustained attention demand), and Probe 2 (80% target probability; increased response inhibition demand). Inactivation of the insula-FC circuit selectively impaired performance during Probe 1 (n = 28 mice; 14 male, 14 female), indicating a role in sustained attention. This deficit was more pronounced in females. To determine whether insula projections to the locus coeruleus (LC) also contribute to attention, we expressed hM4Di in insula neurons projecting to the LC and assessed performance during Probe 1 and Probe 2 in male (n = 14) and female (n = 14) mice. Finally, to characterize the molecular identity of insula-FC projection neurons, we combined viral tracing with single-molecule in situ hybridization (n = 12 mice; 6 male, 6 female). We found that a substantial proportion of insula neurons projecting to the FC were GABAergic, as indicated by expression of Gad1, and that this proportion was higher in females. Together, these findings identify a GABAergic insula-FC circuit that regulates sustained attention and reveal sex-dependent differences in its cellular composition and behavioral function.

Disclosures: O. Frank: None. **H.L. Hallock:** None.

Poster

PSTR376: Attention, Anticipation, and Cognitive Control in Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.14/KK32

Topic: I.01. Attention

Support: ational Institute of Mental Health of the National Institutes of Health, Award Number R01MH123687

Title: Confidence-gated multiple instance learning improves neural decoding, resolving temporal uncertainty and representational drift

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Abstract: Neuronal information processing often unfolds with spatiotemporal dynamics that vary from trial to trial. These dynamics pose a challenge for decoding cognitively relevant information because static decoding approaches may miss relevant information by implicitly assuming constant signal availability. Here we validate a more dynamic decoding framework that addresses two key challenges: non-uniform availability of information within a trial and representational changes of neural information across learning. We propose a novel confidence-gated multiple instance learning (MIL) framework built on a variational autoencoder with a gated-recurrent-unit (GRU) backbone (GR-VAE) to resolve these limitations. The latent manifold is shaped by a multi-task, multi-class classifier with confidence heads for both trial and task that jointly address both forms of uncertainty.
We evaluated the confidence-gated MIL framework on neuronal data from multiple brain areas collected while nonhuman primates performed a learning task where one feature is rewarded out of multiple possible features. To handle temporal ambiguity, the MIL objective for each classification task treats trials as bags of timepoints, combining them by joint softmax pooling. To combat distributional drifts of representations, confidence at the task and trial levels was generated as a label-free measure of information on each classification task and the trial itself, dynamically gating predictions.
We found that across neural recordings from primate anterior cingulate cortex, prefrontal cortex, and caudate nucleus, the model filters out uninformative trials based on task and trial confidence ranking. This enables higher decoding accuracy when evaluated under targeted informativeness thresholds. The learned confidence allows probing of trial-by-trial shifts of information without relying on post-hoc behavioral labeling.
In summary, combining variational autoencoding networks with confidence-gated multiple instance learning provides a versatile decoding approach to address asynchronous, non-stationary neural representations. The proposed framework improves decoding of higher cognitive representations and is suited for brain-computer interfaces aimed at improving cognitive readout.

Disclosures: C.G. Gerrity: None. **T. Womelsdorf:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR377.01/KK33

Topic: I.03. Decision Making

Support: NSF GRFP

Title: Context-dependent information seeking and belief updating in non-human primates

Authors: *S. K. MARKMAN, M. JAZAYERI;
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Abstract: Humans and other animals constantly seek information to guide decisions, anticipate outcomes, and update internal models of the world. Information before a choice can be used to inform actions, after a choice can modify outcome expectations, and after outcomes can expose counterfactuals. Prior work has typically studied these forms of information seeking in isolation, leaving open whether and how shared neural circuit mechanisms flexibly regulate information seeking across decision contexts. To address this question, we developed a novel task for rhesus macaques that affords comparison of information seeking across contexts and enables quantification of how uncertainty, time cost, and counterfactual reasoning shape the decision to seek information. The subject first chooses between two paths, left or right, then pursues the chosen path for approximately 3 seconds before receiving juice or no juice. At any given time, one side is designated the “good” side and is rewarded with 82% probability, whereas the other side is never rewarded. The good side switches unpredictably in blocks of 5-25 trials, with a mean block length of 11.25 trials. On each trial, the subject can reveal information about the reward outcome of one path during one of three epochs: before choosing, during pursuit, or after the outcome. We parametrically controlled the cost of seeking information by varying the time the subject had to spend to reveal it. In one trained animal, information seeking was robustly modulated by both time cost and trial history: the animal sought information less frequently with higher time cost and more frequently with higher uncertainty. The animal used information from all three epochs to update beliefs and guide future choices. The animal was free to switch paths mid-pursuit; revealing a non-reward on the pursued side or a reward on the opposite side prompted switches in a history-dependent manner, giving a behavioral readout of commitment vs. change of mind. A Bayesian observer model fit to behavior indicated that the animal used information to update beliefs substantially, but less than experienced reward outcomes. We are now developing more sophisticated models to quantify how context modulates the influence of information on belief and how expected information gain contributes to the subjective value of information. Building on this behavioral and modeling platform, we aim to record from anterior cingulate cortex, orbitofrontal cortex, and anterior insula using Neuropixels probes to

characterize how these circuits drive context-dependent information seeking and integrate information with experienced outcomes to update beliefs and revise decisions.

Disclosures: S.K. Markman: None. **M. Jazayeri:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR377.02/KK34

Topic: I.03. Decision Making

Title: Inferring internal value functions and model of others with multi-agent inverse reinforcement learning

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Abstract: Social behavior requires individuals to consider not only their own goals, but also the goals, actions, and expectations of others. Internal value functions and beliefs about others' intentions are key determinants of behavior and neural activity, yet these latent representations cannot be directly observed and must be inferred from behavior. Although inverse reinforcement learning can recover latent value functions from behavior in single-agent settings, extending this approach to multi-agent interactions remains challenging because value functions are defined over joint state spaces that grow rapidly with the number of agents. We introduce multi-agent inverse reinforcement learning(MAIRL), a scalable framework for inferring interpretable latent representations of social decision-making through decomposition of joint value functions into individual value maps and low-dimensional interaction terms. This decomposition compactly describes how agents value their own locations, others' locations, and the interaction structure linking them in multiple social foraging tasks. Beyond identifying what agents value, MAIRL can also infer how agents internally predict one another. By treating rewards and task dynamics as known and inferring the partner-prediction strategies that best explain behavior, MAIRL estimates the internal models agents use to anticipate the actions of others, separating social belief inference from reward inference. In simulated social tasks, MAIRL successfully recovered both latent value representations and partner-prediction strategies, revealing distinct internal models even when agents target the same reward. Applied to empirical social behavior, MAIRL reveals reward spatial maps and proximity-based interaction terms in mouse cooperative foraging, distinguishing leader-follower roles and learning-dependent changes in social value. In a non-cooperative primate task, MAIRL uncovers mutual prediction signals related to social hierarchy. Together, these results demonstrate that MAIRL provides an interpretable framework for uncovering both what animals value and how they model the minds of others.

Disclosures: Z. Zhang: None. **Y. Cheng:** None. **M. Kwak:** None. **A. Radulescu:** None. **Z. Wu:** None. **Y. Chen:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR377.03/KK35

Topic: I.03. Decision Making

Title: Computational constraints on cognitive bias in Large Language Models.

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Abstract: Humans exhibit cognitive bias when faced with choices with uncertainty (Tversky & Kahneman 1981). The computational background for the robust effect of framing is an interesting question. Large Language Models exhibit similar bias (Binz & Schulz 2023; Payne 2025). Here we examine a generic mathematical structure inside LLMs, with possible relevance to the cognitive bias. The softmax output carries dual e (natural) and m (expectation) coordinates; value is the log-odds $z=\log(W_A/W_B)$. Gain-framing raises A's weight W_A at per-stimulus rate ρ; loss-framing raises B's W_B at rate ν. Stimulus enters the weights linearly (m) but value is read as logits (e); $\theta=\log W$ makes value/utility logarithmic (Weber-Fechner). With $\beta=\rho/W_A$ and $\gamma=\nu/W_B$, loss aversion $\Lambda=\gamma/\beta=(\nu/\rho)e^{z0}$ equals the base odds e^{z0} when $\rho=\nu$; it is thus a broken gain-loss mirror symmetry ($W_A \geq W_B$ and/or $\nu \geq \rho$).
To avoid format-compliance confounds, we developed the conditional-centroid (CC) method: a probability-weighted average over the response of A/B-intent logits, giving W_A, W_B. Its order parameter $\Phi_{off} = 1 - W_A - W_B$ (off-choice mass) gauges how well an LLM's alignment matches cognitive-science data. Applying prospect theory to Llama-3 via CC: (i) Scale—1B places mass on neither A nor B ($\Phi_{off} \approx 0.99$); 3B separates A/B centroids, β works but $\gamma \approx 0 (\Lambda \approx 0)$; 8B gives $\Lambda \approx 1.89$(16% from human 2.25; TK 1992), base odds $e^{z0} \approx 2.33$ near it. (ii) Training—humility-LoRA on generic MC items (no TK tasks) lifts the loss branch 3B lacked to 8B; moderate intensity reaches $\Lambda \approx 2.37$, overtraining reverses β . (iii) $\Phi_{off} \in [0.1, 0.7]$ is the linear-response regime for Λ ; 8B-naive (0.39) and C1-humility (0.60) lie within. Based on a series of analysis, we discuss the constraints on cognitive biases from output-manifold geometry and operationalizing. Our analysis shows how generic properties of LLMs possibly constrain cognitive bias. By referring to results from mechanistic interpretability (Olah et al. 2017 2020), we discuss implications of linkage (Vilas et al. 2024) to cognitive neuroscience.

Disclosures: Y. Tamori: None. **K. Mogi:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR377.04/KK36

Topic: I.03. Decision Making

Support: NIH Grant R01MH128344
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Title: Why do we seek information about the future? On the origins of subjective value without instrumental value

Authors: *E. S. BROMBERG-MARTIN[1], J. MEREL[3], F. SOGUKPINAR[4], I. E. MONOSOV[2];
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Abstract: Why do we want to know the future? Humans and many animals pay for information to predict uncertain rewards, even when they cannot control them. The reason for this conserved yet seemingly paradoxical preference - “subjective value without instrumental value” - remains unknown. Here we develop a normative framework to explain the origin of such preferences, their persistence across species, and their contributions to survival. We formalize and evaluate theories that explain information’s subjective value as originating as an adaptive estimate of its advantage for solving core computational problems posed by natural environments. One theory, which we call Time Allocation (TA) theory, proposes that information helps organisms in nature improve their time allocation during foraging (Vasconcelos et al., 2015). A second theory, Credit Assignment (CA) theory, proposes that information helps organisms solve the temporal credit assignment problem during reinforcement learning (Bromberg-Martin and Hikosaka, 2009). We embody each theory with a computational model of an optimal Bayesian agent maximizing reward in a naturalistic environment. We then compute the instrumental value of information in each model, and test whether it predicts the true subjective value of information measured experimentally in humans and monkeys (Bromberg-Martin and Feng et al, 2024). We show that these theories operate through distinct mechanisms, yet remarkably, both make a series of common, correct, detailed predictions about human and animal subjective values. This suggests that organisms may place subjective value on information in order to help them to solve both the TA and CA problems simultaneously in nature. We further leverage our framework to derive novel types of information making it possible to dissociate these theories and test if organisms use a mixture of both to compute their subjective values. Indeed, we show that mixed value computations combining both theories achieve the highest performance across diverse naturalistic environments. Finally, we provide evidence that the theorized benefits of information can also apply to artificial neural network (ANN) agents for reinforcement learning, substantially improving both training speed and performance. Thus, our work provides new evidence that organisms compute the subjective value of information in a manner that is non-instrumental in

experimental tasks but is conserved across species and well suited to guide adaptive behavior across a range of natural environments.

Disclosures: E.S. Bromberg-Martin: None. **J. Merel:** None. **F. Sogukpinar:** None. **I.E. Monosov:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR377.05/KK37

Topic: I.03. Decision Making

Support: ERC MYODECISION (101077772)

Title: Exploring the Influence of Motor Effort on Perceptual Decision-Making

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Abstract: The response-reporting action is often treated as a downstream consequence of a decision, whereas its motor requirements—which may also shape decision formation—are rarely considered. Response-force manipulations have often been modelled behaviorally as affecting non-decision time and, less consistently, boundary separation (Sandry et al., 2022). EMG work suggests that decision processes continue through motor execution, with evidence-independent urgency supporting effortful responses under weak evidence or time pressure (Edouard et al., 2025). Here, we examined EEG signatures of perceptual decision formation to probe response-force effects on the perception-to-action pathway. Twenty-seven participants judged the tilt direction of a visual stimulus while responding with low or high force under crossed contrast and time-pressure conditions, with force initiation and completion measured.
Behaviorally, time pressure and contrast strongly modulated accuracy and response timing. Force did not clearly affect accuracy or force initiation times, but robustly lengthened the force onset-to-threshold interval, increasing final force-threshold response time. At the neural level, force requirements did not reliably modulate CPP or SSVEP activity, suggesting that response force did not strongly alter sensory evidence representation or the centro-parietal decision-formation signal. In contrast, build-to-threshold effector-selective motor preparation (mu-beta desynchronisation) showed a clear force-dependent effect before evidence onset, when it is thought to reflect response caution (Kelly et al., 2021). Dynamic anticipatory buildup (indicative of urgency) was evident in all conditions, but high-force trials showed lower mu-beta amplitude during the 600ms period preceding evidence onset ($F(1,26) = 6.23$, $p = 0.019$), consistent with stronger anticipatory motor preparation. This effect was present under both high and low time pressure.
Together, the behavioral and EEG findings suggest that physical effort does not simply impose a post-decisional motor cost. Rather, they are broadly consistent with EMG-informed accounts in

which response-force demands increase motor urgency. Our EEG data provide further insight into the dynamics of this urgency, showing that high-force requirements were associated with a pre-evidence starting-point shift in effector-selective motor preparation, before the initiation of a dynamic buildup that was common to all conditions. Thus, expected effort may establish an anticipatory motor state before evidence onset, shaping how an emerging decision is translated into action.

Disclosures: W. Lian: None. **E.A. Corbett:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR377.06/KK38

Topic: I.03. Decision Making

Support: NIH ZIA MH002983

Title: Computational Dissection of Probabilistic Reversal Learning in Rats Reveals Contribution of Hippocampal Neurogenesis to Adaptive Behavior

Authors: *V. CALIA-BOGAN[1], K. B. HUNTZICKER[4], E. GARR[2], H. A. CAMERON[5], A. LANGDON[3];
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Abstract: Adult hippocampal neurogenesis (AHN) occurs naturally and is associated with learning; inhibition of AHN alters performance in a broad range of behavioral tasks, though identifying the specific cognitive processes underlying these effects remains difficult (Yau et al., 2015). Here, we use a reinforcement learning model (Q-learning) to interrogate the specific behavioral differences in wild-type (WT, n = 25) and transgenic AHN-inhibited (TK, n = 31) rats during a probabilistic reversal learning (PRL) task. Following the procedure in Snyder et al. 2016, TK rats (Long-Evans background) and WT Long-Evans rats were allowed to reach maturity and then treated with the antiviral drug valganciclovir for 8 weeks, resulting in complete AHN-inhibition only in TK rats. Following treatment, performance across 25 sessions of a 2-choice PRL task was evaluated. Each PRL session consisted of 200 trials, with high reward probability choice reversing sides every 40 trials. Every session began with the same side high (0.8) and low (0.2) reward probability choice. Analysis of behavioral performance revealed that both TK and WT groups increased in accuracy across sessions, with performance at chance during the first session and reaching 15-20% above chance by session 25 (excluding first pre-reversal block). Notably, TK rats received significantly more rewards compared to WT rats. Furthermore, TK rats showed significantly more exploitation in the form of increased win-stay probabilities. We probe these group differences further with four classes of Q-learning models,

fitting separately for TK and WT groups and evaluating each fit via Akaike Information Criteria and Bayesian Information Criteria. All models include learning rate, inverse temperature, and side bias, while more complex models introduce perseveration, lapse (measuring evidence-independent choice repetition), and cross-session learning effects. The best-fitting Q-learning model for each group included the full set of parameters, with fit learning rates for TK rats significantly higher than WT rats and increasing monotonically over the sessions, while choices in the WT rats had a significantly higher lapse rate than TK. We conclude that AHN inhibition in rats does not necessarily impair learning or performance in this PRL task per se, but does influence how learning and performance evolves across extended experience in this probabilistic choice task.

Disclosures: V. Calia-Bogan: None. **K.B. Huntzicker:** None. **E. Garr:** None. **H.A. Cameron:** None. **A. Langdon:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR377.07/KK39

Topic: I.03. Decision Making

Support: ARO MURI grant W911NF2110328

Title: Bayesian Inference of Latent Context Regulates Goal Commitment and Navigation under Uncertainty

Authors: *A. MARINKOVIC, S. AENUGU, J. P. O'DOHERTY;
Caltech, Pasadena, CA

Abstract: Context shapes the goals that agents pursue in an environment. However, context is often latent rather than directly observable, requiring inference to determine which goals are relevant for adaptive behavior. How the inference of latent contextual states influences the valuation of states and actions to support autonomous goal-directed behavior remains poorly understood. While previous studies have examined latent-state inference or goal-directed navigation in isolation, our study aims to investigate how inferred contextual beliefs dynamically regulate commitment to goals and the execution of navigational policies.
To address this question, we developed a naturalistic 3D maze-navigation paradigm in which participants navigate through clue rooms in a castle to infer which of three latent contexts is currently active and subsequently navigate to the destination associated with that context. Participants (n = 60) identified the active context with high accuracy across rounds, and their beliefs about the latent context systematically influenced navigational decisions. Specifically, participants' commitment to a goal destination and their navigational vigor increased as their belief in a particular context strengthened. Moreover, dwell times within clue rooms were consistent with Bayesian belief-updating processes, suggesting that participants

actively integrated contextual evidence before committing to a goal. At the group level, behavior was well captured by a hierarchical Bayesian reinforcement learning model in which a high-level agent infers context and selects goals, while a low-level agent executes context-dependent navigational policies. The model successfully reproduced participants' probability of committing to a goal across varying levels of contextual uncertainty.
Building on this behavioral framework, our ongoing fMRI study aims to identify the neural substrates supporting the hierarchical computations captured by the model. In particular, we seek to dissociate the neural representations of the high-level and low-level agents and to characterize the roles of the hippocampus and prefrontal cortex in encoding contextual identity and uncertainty. More broadly, this work aims to reveal how the brain uses inferred context to dynamically shape state-space valuation and facilitate autonomous goal-directed behavior in uncertain and ambiguous environments.

Disclosures: A. Marinkovic: None. **S. Aenugu:** None. **J.P. O'Doherty:** None.

Poster

PSTR377: Computational Models of Decision-Making

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Topic: I.03. Decision Making

Support: NIBIB R01EB029857
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NINDS R01NS115327

Title: Latent decision signaling in mouse PPC in accumulation of somatosensory evidence

Authors: *D. A. WEISS[1], A. M. F. BORSA[2], A. KIM[3], C. WAIBLINGER[2], G. B. STANLEY[2]; [1]Wallace H Coulter Dept. of Biomed. Engin., [2]Coulter Dept. of Biomed. Engin., [3]Bioinformatics Grad. Program, Georgia Inst. of Technol., Atlanta, GA

Abstract: As we explore and interact with the world, most perceptions and decisions require integration of many pieces of evidence collected over a period of time. However, even after two decades of studies on evidence accumulation, it is still unclear how neuronal populations cooperate to dynamically accumulate evidence over time towards perceptual decisions, and to what extent these decision signals are separable from pure sensory and motor signals. To address this gap, we trained mice to perform a two-alternative forced choice task that requires accumulation of somatosensory evidence over time with a delay period separating decision formation from reporting. Animals were exposed to trains of discrete, Poisson distributed random whisker stimuli to both sides of their face and tasked to discriminate which side received the higher number of stimuli over a 1 sec window, indicated through licking either left or right water ports at least 250 ms after stimulus offset. While animals performed the task we recorded

population spiking activity in a multisensory posterior parietal cortical (PPC) region of the mouse (Rostrolateral, or RL) using silicon electrodes. PPC has previously been shown to contain correlates of decision-making with varied success in affecting decision-making behavior through inhibition studies, depending on sensory modality and PPC subregion targeted. Here we show that the neural population in RL accumulates subjective decision information on a subspace that is separable from both pure sensory and motor information. This area encodes animal choice more strongly than pure sensory information, and undergoes a rapid change in choice encoding from pre-movement to movement periods. By isolating choice-specific activity using targeted dimensionality reduction, we find signatures of ramp-to-choice dynamics underlying the neural activity. Additionally, unilateral inhibition of RL causes a contralateral behavioral bias, indicating that RL is necessary for this somatosensory accumulation of evidence behavior. In ongoing work, we are modeling the underlying accumulation process with latent variable models to estimate moment-by-moment decision variables, providing potential opportunities for real-time manipulation and optimal control of decision making.

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Poster

PSTR377: Computational Models of Decision-Making

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Topic: I.03. Decision Making

Support: National Research Foundation of Korea (NRF), RS-2023-00264409
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National Research Foundation of Korea (NRF), RS-2025-00522868

Title: Motif-based hierarchical rule inference in recurrent neural networks

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Abstract: In hidden-rule environments where only input-output relationships are observable, agents must determine which rule hypothesis to evaluate next. Conventional approaches, including Bayesian inference and reinforcement learning, treat candidate rules as independent hypotheses. We instead propose that the rule space possesses a hierarchical structure organized by shared computational properties, or dynamical neural motifs. Under this framework, rules sharing motifs can be supported or rejected together. Motif-based inference assists rule-based inference and reduces representational change, potentially offering a more biologically plausible strategy. We modeled rule inference using an agent comprising a Gumbel-softmax rule selector, a pretrained multitask RNN rule executor, and a confidence updater. Three updater variants were

implemented: a multilayer perceptron (MLP) baseline, a rule-evidence updater, and a motif-based updater. Within each session, a single hidden rule governed the stimulus-response mappings, and the agent inferred it through trial and error. Dynamical motifs were identified from RNN activity by quantifying fixed-point continuity, stability, and state trajectory overlap across rule pairs via linear interpolation, then integrated into a rule-by-motif membership. Two independently trained models were evaluated across 15 cognitive rules with 240 sessions per updater condition. All models were trained with a penalty on hidden-layer representational change. The MLP updater achieved 97.5% task success and reached the criterion in 14.3 ± 1.1 trials. We set the MLP model as an approximate ideal agent, where rule-based and motif-based updaters were compared. Rule-based and motif-based updaters showed comparable task performance (80.4% and 76.7%) and similar trials-to-criterion (45.5 ± 1.5 vs. 45.5 ± 1.6). However, MLP confidence dynamics were overall more closely aligned with motif-based than rule-based updates (Wilcoxon signed-rank test, $p < 0.05$). On trials where rule-based updates diverged from MLP dynamics, motif-based alignment increased (Wilcoxon signed-rank test, $p < 0.001$). Motif-based updates also showed numerically smaller hidden-layer representational change, though not statistically significant. We anticipate that testing with broader random seeds, stricter capacity constraints, or a biologically inspired PFC-BG model as the baseline may yield more robust effects. These findings suggest that RNN-based agents exhibit confidence dynamics consistent with motif-level hierarchical organization, supporting that dynamical motifs may be part of functional units guiding hypothesis search.

Disclosures: H. Lee: None. **E. Chung:** None.

Poster

PSTR377: Computational Models of Decision-Making

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Program #/Poster #: PSTR377.10/KK42

Topic: I.03. Decision Making

Support: P50MH132642
RO1 EY017699
R01MH137624

Title: Hidden Rule Changes Reveal the Anatomy of Human Flexibility

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Abstract: Adaptive behavior often depends on inferring that a previously learned rule no longer works. Accuracy recovery captures the outcome of this adjustment, but not the choice components that produce it. After a hidden rule change, the same accuracy can reflect old-rule

carryover, current-rule support, costly search-like responding, or sensory/lapse variability.We tested this in a feedback-guided color-category mapping task. Participants learned the active mapping and inferred covert switches. Rather than scoring choices only as correct or incorrect, we classified each response by the mapping it matched. Post-switch errors were dominated by old-rule choices, while recovery reflected declining old-rule responding and rising current-rule responding. We then asked whether mapping-space size changed these components. The 3-mapping task constrained covert switches to three viable mappings. The 6-mapping task preserved the same switch logic but allowed six viable mappings, including reverse/flip alternatives. In high-strength trials, the 6-mapping task increased early novel/off-rule choices (+6.9 percentage points; 95% CI [3.3, 9.9]), with the increase concentrated in reverse/flip transitions. These choices were slower and were followed by higher next-trial current-rule responding, consistent with costly local diagnostic updating rather than a general benefit of exploration. Across the two experiments, late old-rule residuals were similar after equal-strength/relative-trial standardization (+1.2 percentage points; 95% CI [-0.6, 2.9]). Thus, the larger mapping space increased early search-like demands without measurably compromising later suppression of the no-longer-valid old mapping.As a complementary test, neural-agent analyses asked whether task success was sufficient for human-like choice dynamics. In the more demanding 6-mapping setting, an engineered fast-trace MLP-oracle positive control reached human-comparable late accuracy, but produced far fewer old-rule choices among post-switch errors than humans did (16.1% vs. 93.4%). GRU-style recurrent controls showed old-rule carryover but weak recovery. We used a task-scaled Bayesian observer (TSBO) as a model-based benchmark for comparing human choices with DNN policies. In calibrated policy-transfer tests, TSBO assigned higher likelihood to human choices than the DNN policies did.Together, these findings characterize human flexibility after hidden rule changes as structured shifts in persistence, updating, transition-sensitive search-like responding, and residual choice variability—components that accuracy recovery alone conceals.

Disclosures: J. Huang: None. **L. Ying:** None. **M. Halassa:** None. **A.G. Collins:** None. **S. Kastner:** None.

Poster

PSTR377: Computational Models of Decision-Making

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Program #/Poster #: PSTR377.11/KK43

Topic: I.03. Decision Making

Title: Individual differences in information-seeking strategies affect decision-making in unstable environments

Authors: *J. BAKER[1], J. I. GOLD[2], J. BOSULU[3];
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Abstract: Effective decision-making in uncertain and unstable environments relies on flexible forms of evidence accumulation that adapt to environmental dynamics. The flexibility involves accumulating all relevant evidence to reduce uncertainty when it is high but only contradictory evidence to account for changes in the environment when uncertainty is low. These flexible accumulation processes have been studied using task conditions in which relevant evidence is presented sequentially and exclusively. Here we examined how these processes relate to information-seeking behaviors when the source of relevant evidence is more ambiguous. Human participants made ongoing judgments about which of two sources was responsible for generating sequences of noisy observations. The sources were modeled by normal distributions with identical standard deviations but different means, corresponding to distinct locations on the screen. The evidence was generated as independent samples from the generative source and presented as a "T". Distractors (20 "L"'s) were randomly positioned to add noise. The target and distractor positions were updated every 50 ms. We controlled task difficulty by adjusting the standard deviation of the generative source distributions, the density of distractors, and the (fixed) rate at which the generative source switched between the two distributions. We monitored each participant's gaze using a video eye-tracking system to infer their information-seeking strategies. In a preliminary dataset (N = 8), we observed substantial individual differences in the strategies participants used that were related to overall performance. In easier conditions, participants who spent the majority of time looking at the sources (N = 5) tended to have the best overall performance (99% correct, maximum rate of accuracy change = 0.58 units/s). Conversely, in more difficult conditions participants who used this strategy (N = 4) tended to have lower performance (67%, 0.12) than those who spent slightly more time looking at more ambiguous regions (91%, 0.18, N = 3). Despite individual differences, we found that participants used strategies that depended on uncertainty. When uncertainty increased, most participants increased the proportion of time spent looking for evidence where the source distributions overlap compared to looking directly at one of the sources (N = 7). Together these findings show that people use idiosyncratic, adaptive information-seeking strategies when the source of relevant evidence is unknown. Ongoing work is relating these strategies to the overall goal of mitigating uncertainty when it is high and refining belief accuracy when it is low.

Disclosures: J. Baker: None. **J.I. Gold:** None. **J. Bosulu:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR377.12/KK44

Topic: I.03. Decision Making

Support: PhD program "Sciences of the mind", Università degli studi della Campania "Luigi Vanvitelli"

Title: Bridging Perceptual Inference and Reinforcement Learning: A Novel RLDDM Approach to Sensory and Category Information.

Authors: *A. SOSPEDRA ORELLANO[1,2], I. OBESO[1];
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Abstract: Recent studies indicate that striatal dopaminergic activity (sDA) does not only encode reward prediction error signals (RPEs), but also regulates learning rates and integration timescales, affecting both perceptual inference and reinforcement learning (RL). Evidence also suggests that recency biases are driven by stimulus perceptual strength (sensory information, SI), while primacy biases are driven by frequency with which evidence favors a response option (category information, CI) — both mediated by discount rate adjustment. Hence, we investigated how SI and CI may interact with RL mechanisms to promote efficient decision making and learning. We conducted a behavioural (n=105) and neuroimaging study (n=45) where participants identified the dominant color in sequences of 10 static dot clouds (red or blue) and rated their confidence. Virtual coins were rewarded if correct and lost if too slow. We manipulated both SI (difference of red - blue dots) and CI (ratio of red/blue frames). Analyses included reverse correlation to compute integration kernels. We fitted a novel reinforcement learning drift diffusion model (RLDDM) whose parameters varied according to SI and CI levels, as well as average expected reward and RPE size. We consistently found U-shaped integration kernels, not predicted by previous models. Concurrently, recency increased with the size of the SI-CI difference, task progression (number of answered trials) and accuracy. In our RLDDM, CI signaled prior strength through a negative leakage (confirmation bias), and SI and task progression signaled discriminability, thereby increasing drift rate and positive leakage. Notably, the RL learning rate decreased with average expected reward (model confidence) and increased with RPE size. Therefore, our RLDDM transcends classical meta-learning by mechanistically unifying Bayesian perceptual inference and reinforcement dynamics. By demonstrating how sensory evidence and prior knowledge dynamically tune integration and learning rates. This unified framework not only resolves the origins of complex temporal biases, but also establishes a powerful foundation for identifying computational markers of dopaminergic cortico-striatal contributions to adaptive decision-making.

Disclosures: A. Sospedra Orellano: None. **I. Obeso:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR377.13/KK45

Topic: I.03. Decision Making

Title: A Dual-Controller Model of Human Probabilistic Learning Based on Reward and Action Prediction Errors: Insights from Neuromodulation and Computational Modeling

Authors: A. SOSPEDRA[1,3], R. AVILA GARCIA[2], J. ORTEGA[3], M. ESCRIBANO RODRÍGUEZ[4], ***I. OBESO**[5];

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Abstract: Habit formation in humans emerges from the interaction between reward-guided choice and the progressive stabilization of stimulus-action associations. It remains debated whether these components rely on shared or dissociable mechanisms. Recent experiments in rodents demonstrate that phasic frontostriatal dopaminergic signals not only encode reward prediction errors (RPEs), but also action prediction errors (APEs). Yet, limited evidence is available on the cortical causal implications to both learning signals, particularly during tasks requiring complex motor responses. To investigate this, 22 healthy participants performed a probabilistic reward-learning task, selecting between two visual stimuli via continuous joystick movements. One stimulus carried a higher reward probability within each block, with contingencies changing unpredictably across blocks. Reward delivery was conditional on successful choice and motor execution. We tested three cortical conditions using single-blind inhibitory transcranial static magnetic stimulation (tSMS): real and sham stimulation of the medial prefrontal cortex (PFC), and real stimulation of the parieto-occipital cortex (PO). We developed a novel dual-controller reinforcement learning model combining a value-learning component and an action-history component, updated through RPEs and APEs, respectively. Model comparisons strongly supported the dual-controller account. Value updating was gated by motor success. Although tSMS conditions did not significantly affect overall behavioral performance, PO inhibition increased the learning rate of the action-history component. These findings support the idea that human probabilistic learning depends on dissociable value-learning and action-stabilization processes. More broadly, they provide evidence that distinct cortical systems contribute to reward-guided learning and action stabilization during complex, non-ballistic motor behavior, helping bridge animal models of learning with human decision-making.

Disclosures: A. Sospedra: None. **R. Avila Garcia:** None. **J. Ortega:** None. **M. Escribano Rodríguez:** None. **I. Obeso:** None.

Poster

PSTR377: Computational Models of Decision-Making

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Program #/Poster #: PSTR377.14/KK46

Topic: I.03. Decision Making

Support: Jessamine K. Hilliard Fellowship

Title: State-dependent input gain modulation toggles cortical decision-microcircuits between sensory-coupled and sensory-decoupled regimes.

Authors: *L. YE[1], A. K. CHURCHLAND[2];
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Abstract: Sensory-guided decision-making is influenced by fluctuations in behavioral states, but the circuit-level mechanism that distinguishes these strategies is unknown. Prior literature suggests that simultaneous, multiplicative modulation of excitatory (E) and inhibitory (I) gains is sufficient to interpolate between integration, biased-integration and competition regimes, but this has not been tested against trial-resolved choice data from individual animals. We trained wild-type C57BL/6J mice (WT; n=6) to perform a freely moving two-alternative forced-choice audiovisual rate-discrimination task and fit a four-state Bernoulli GLM-HMM to identify engaged, left-bias, right bias, and low-sensitivity latent states. We then trained a Dale's-law E/I recurrent neural network per mouse to predict binary choice from trial stimulus and parameterized the network such that state modulation entered through seven multiplicative parameters: recurrent E/I gains, sensory input gain, leak (α), noise (σ). Results show that excitatory and inhibitory unit populations lose choice tuning in low-sensitivity states, and that inhibitory units are more strongly modulated by choice compared to excitatory neurons across all engaged states, as predicted by inhibition-stabilized circuit theory. Input gain shows a decrease in both bias states, as well as a statistically significant ($p=4.6\times10^{-6}$) collapse in low-sensitivity states - establishing a state-specific, input-gating switch rather than a graded modulation. As behavioural states are also jointly shaped by neuromodulators, we then asked how perturbed dopaminergic tone may affect the microcircuit. To address this, we repeated these analyses on a cohort of heterozygous dopamine-transporter knockout mice (DAT+/-; n=6), an animal model of ADHD. DAT +/- mice reproduced input gain collapse but interestingly showed significantly elevated noise (σ) levels ($p=0.024$) in low-sensitivity states, suggesting a potential dopamine-specific modulation axis. Together, these results identify state-dependent multiplicative input gating, not additive offset, as the mechanism by which a cortical-microcircuit architecture toggles between sensory-coupled (engaged, biased) and sensory-decoupled (low-sensitivity) computational regimes, acting as a bridge between latent behaviour and circuit dynamics that is directly testable with cell-type-specific gain perturbations.

Disclosures: L. Ye: None. **A.K. Churchland:** None.

Poster

PSTR377: Computational Models of Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR377.15/KK47

Topic: I.03. Decision Making

Support: Jane Coffin Childs - HHMI Fellowship
Gordon Center for the Cure and Treatment of Paralysis
Hearst Fellowship

Title: Time to Stop: Insular-Prefrontal Circuit Mechanisms of Self-Generated Stopping Decisions

Authors: *S. LIU, B. L. SABATINI;
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Abstract: Many decisions are self-generated: the brain must infer the state of the environment and decide when to act without explicit external cues. Although such decisions have been studied at behavioral and computational levels, how the underlying computations are implemented by neural circuits remains unclear, in part because sensory, motor, and cognitive variables are often tightly entangled. To isolate these variables in a reductionist setting, I focused on a simple but important problem: how the brain decides when to stop an ongoing action when an expected reward fails to occur. To address this question, I developed a behavioral paradigm in which thirsty mice lick a spout several times to trigger a water reward, delivered on half of the trials and omitted on the other half. On omission trials, licks before and after the trigger-lick produce nearly identical sensory input and motor output, so stopping cannot be driven by an external signal. Instead, it must arise from an internal comparison between current sensory evidence ("no water") and an expectation of reward ("water should have arrived by now"), generating a mismatch signal that triggers stopping. Using large-scale Neuropixels recordings, I found a division of labor across two cortical regions. Insular cortex (IC) carries a bidirectional water-versus-no-water signal that tracks manipulations of reward timing and magnitude. By contrast, at stopping, the medial prefrontal cortex (mPFC) enters a distinct neural state, and optogenetic silencing of mPFC delays stopping, supporting a causal contribution to the stopping process. Ongoing analyses of joint recordings reveal directional influence from IC to mPFC during different epochs of the trial. Together, these findings suggest a candidate circuit motif in which an early mismatch signal is converted into a self-generated stopping decision, providing a tractable framework for studying how internal computations are translated into actions.

Disclosures: S. Liu: None. **B.L. Sabatini:** None.

Poster

PSTR377: Computational Models of Decision-Making

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Program #/Poster #: PSTR377.16/KK48

Topic: I.03. Decision Making

Support: NIH R01 DA047870
ZIA MH002928

Title: Flexible timescales of neural response in the prefrontal cortex

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Bethesda, MD; [3]Neurosci., Johns Hopkins Univ. - Main Campus, Baltimore, MD; [4]NIMH/NIH, Bethesda, MD

Abstract: There is recent evidence that timescales of individual neural response serves as an organizational principle of cortical computations across mammalian brains, in which brain regions higher in cortical hierarchy integrate information at longer timescales (Murray et al., 2014; Spitmaan et al., 2020; Song et al., 2024). Yet, it remains largely unknown whether these timescales are flexible such that information more relevant for behavior is integrated at different timescales. Especially, neurons in the prefrontal cortex exhibit highly heterogeneous timescales in their response, raising the possibility that these timescales could be sensitive to given context and task demands. To examine this, we performed high-density recordings of lateral prefrontal cortex activity in monkeys performing a dynamic learning task with uncertainty about which choice attribute is relevant for a given environment (stimulus identity vs. location). We hypothesized that the choice memory relevant for the monkeys' current strategy is enhanced at a single-neuron level to increase the impact of corresponding information on choice behavior. To this end, we applied a comprehensive method that simultaneously estimates multiple timescales of an individual neuron (Spitmaan et al., 2020; Trepka et al., 2024). For each cell (n=6131), we validated whether its activities are characterized with memory traces for chosen stimulus or chosen action during each block of trials. We then compared the estimated timescales between two block types which had different choice rules (stimulus- vs. action-based) unknown to the monkeys. We found that the memory timescales across PFC neurons were significantly affected by whether given choice attribute were relevant for predicting rewards on a given block of trials. More specifically, memory timescales for chosen action (τ_{action}) were significantly larger during 'Where' blocks in which choice location is the correct attribute for obtaining reward, compared to 'What' blocks in which stimulus identity is the correct attribute (β=-1.56, p<.001; 15.9% of cells; main effect of block type in mixed-effects model). Similarly, memory timescales for chosen stimulus ($\tau_{stimulus}$) was significantly larger during 'What' blocks compared to 'Where' blocks (β=2.38, p<.001; 12.5% of cells). Interestingly, reward memory timescales (τ_{reward}) were larger during 'Where' blocks than 'What' blocks, similar to choice action timescales but to a lesser degree (β=-0.19, p<.001; 32.8% of cells). Overall, these results suggest that task-related timescales in PFC are not fixed but instead, are flexibly adjusted to task context at a single neuron level.

Disclosures: J. Woo: None. **R. Bartolo:** None. **D. Lee:** None. **B.B. Averbeck:** None. **A. Soltani:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR378.01/KK49

Topic: I.07. Long-Term Memory

Title: Retrieval Goals Shape Memory Representations Across Brain Regions And Over Time

Authors: *E. GHIRALDINI[1], S. A. MORGAN[1], S. D. ALLEN[5], C. A. DAVIS[2], I. A. DIONNE[6], Y. H. SILVA[3], C. B. MARTIN[4];
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Abstract: Evidence from prior neuroimaging studies suggests that hippocampal representations of prior experiences are not fixed. Different studies report increased similarity, orthogonalization, or decreased similarity across memories sharing the same context. One factor that could explain these contrasting findings is retrieval demands: when retrieving the gist of an experience (e.g., my entire trip to Rome), we would expect greater similarity in hippocampal activation patterns of related memories, whereas retrieving detailed experiences (e.g., the specific visit to the Colosseum) should produce reduced neural similarity between the same event representations. Another question concerns the stability of these memory representations over time and how they are affected by sleep-dependent consolidation. Some studies suggest that the similarity between related memories increases over time, while others report the opposite pattern. In this study, we aimed to examine how retrieval demands shape memory representations over time and how sleep-consolidation mechanisms interact with retrieval goals. Two samples of twenty-five healthy young adults watched two unrelated episodes of the sitcom Seinfeld. During functional magnetic resonance imaging (fMRI) scanning, they were asked to recall different levels of specificity: specific scenes, a character's narrative in an episode, or the main plot of an episode. The first group performed the fMRI task immediately after encoding, the second group after a 48-hour delay. A pattern-based similarity analysis of neural data from the immediate retrieval group revealed significant differences between conditions in the hippocampus (HPC) and parahippocampal cortex (PHC), but not in the medial prefrontal cortex (mPFC). In the HPC, episode recall showed the highest degree of neural differentiation, followed by narrative, and scene recall, whereas the PHC showed the opposite pattern. These between condition differences were not apparent in the HPC after a 48-hour delay, but did persist in PHC. Interestingly, a difference did emerge in mPFC after a delay. Specifically, we found that episode recall was associated with differential integration in this region. These findings suggest that memory representations are shaped by retrieval goals and expressed differently across brain regions and time. They also offer a potential explanation for the conflicting evidence found in previous studies.

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Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

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Program #/Poster #: PSTR378.02/KK50

Topic: I.07. Long-Term Memory

Support: Medical Research Council Doctoral Training Program in Precision Medicine (MR/W006804/1 to E.M.)
D.B. is supported by a UKRI Frontier Research grant (EP/X023060/1)

Title: Non-invasive tracking of hippocampal theta oscillations

Authors: *E. MARCANTONI[1], D. WANG[2], C. DAUBE[1], R. INCE[3], L. T. PARKKONEN[4], S. PALVA[5], D. BUSH[6], S. HANSLMAYR[2];
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Abstract: Hippocampal theta oscillations play a crucial role in the formation of episodic memories by binding multisensory information into coherent episodes. Brain stimulation studies suggest that memory performance can be modulated by targeting theta oscillations, offering potential translation for treating memory disorders. However, to effectively engage theta oscillations precise knowledge about the presence, frequency and location of these oscillations is required which has been a challenge particularly for non-invasive methods such as MEG.
Here, we provide evidence that hippocampal signals are visible in MEG sensors, and propose an MEG-based analysis pipeline to track oscillatory hippocampal theta dynamics over time.
To assess hippocampal contributions to MEG measurements, we analysed a simultaneous MEG-iEEG dataset. Using canonical correlation analysis (CCA) in a data-driven approach, we identified shared components that were temporally, spectrally, and spatially aligned across modalities, indicating clear hippocampal contributions to the MEG signal. Notably, leveraging the biophysical priors of classical spatial filtering together with a univariate cross-correlation approach also recovered spatially specific hippocampal signatures.
To validate the ability of the pipeline to detect genuinely oscillatory theta signals, we first applied it to a rodent dataset and replicated the well-established correlation between theta frequency and running speed. We then tested the pipeline on human MEG data recorded during 4 Hz rhythmic sensory stimulation, demonstrating that the estimated hippocampal frequencies shifted significantly toward the stimulation frequency during the stimulation window. Finally, applying the pipeline to the simultaneous MEG-iEEG dataset, we demonstrated an above-chance correlation between theta frequencies estimated from MEG and those directly measured from hippocampal iEEG.
These findings provide evidence that MEG can reliably track individual hippocampal oscillatory dynamics, paving the way for future non-invasive closed-loop interventions that adapt stimulation frequency and timing to ongoing oscillations.

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Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

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Program #/Poster #: PSTR378.03/KK51

Topic: I.07. Long-Term Memory

Support: NIH IRP 1ZIANS002977
NIMH/NINDS Functional MRI Facility

Title: State-dependent TMS modulation of resting-state theta-gamma coupling

Authors: L. E. KONS[1], E. M. WASSERMANN[1], *K. N. WARREN[2];
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Abstract: Episodic memory allows us to reflect on the past, make decisions about the future, and form a learned identity. It depends on the hippocampus as well as on the distributed set of regions which form the hippocampal-cortical network (HCN). Activity within this network is coordinated via hippocampal theta coupled with cortical gamma rhythms, and transcranial magnetic stimulation (TMS) targeted to this network and delivered to mimic this theta-gamma coupling has been used to modulate HCN activity and improve memory performance. However, activity in this network is altered by engagement in memory tasks and it remains unknown whether and how these changes in network state may alter the response to stimulation. We used an online TMS paradigm to investigate how neural state at the time of stimulation influences the effect of TMS on memory and the electrophysiological signatures of HCN activity and connectivity. Participants (n=32) were shown objects in one of four locations and instructed to remember the objects and their locations for later testing. Across four task blocks, trains of theta-burst TMS were delivered either prior to or immediately after stimulus onset to either a subject-specific HCN-node in lateral parietal cortex or a control site at the vertex. Resting-state EEG was collected at baseline and after each TMS/task block to analyze the impact of HCN-targeted vs. vertex stimulation, before vs. during-trial stimulation, and their interaction on theta-gamma phase amplitude coupling and its relationship to TMS-induced memory improvement. HCN-targeted TMS enhanced memory performance relative to vertex TMS when delivered with the trial stimulus, relative to TMS before trial onset. This was coupled with state-dependent modulation of theta-gamma phase-amplitude coupling in post-TMS rest. Broadly, there was a main effect of location on the theta-gamma modulation index over left parietal electrodes near the HCN target, suggesting increased entrainment of HCN-targeted TMS regardless of timing. But the specific theta phase of modulation varied based on the timing of TMS delivery, with more specific phase-dependency when HCN-targeted TMS was delivered with the trial stimulus. This suggests that engagement in encoding makes the HCN-network more susceptible to oscillatory entrainment with behavioral consequences. Further, TMS modulates memory performance in a network-specific, task-dependent manner, arguing for controlling neural and behavioral state at the time of TMS delivery in future studies.

Disclosures: L.E. Kons: None. **E.M. Wassermann:** None. **K.N. Warren:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR378.04/KK52

Topic: I.07. Long-Term Memory

Title: Directed hippocampal effective connectivity across episodic memory tasks

Authors: *S. ZAFARMANDI ARDABILI[1], T. PRUITT[2], C. DAVILA[1], B. C. LEGA[3]; [1]Southern Methodist Univ., Dallas, TX; [2]Radiology, [3]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX

Abstract: The anterior and posterior hippocampus make distinct contributions to episodic memory, and prior intracranial studies have demonstrated functional connectivity along the hippocampal long axis during memory processing. However, less is known about how directed, frequency specific interactions between hippocampal subregions are modulated by memory success and whether these interactions differ across memory tasks. To address this question, we used induced response dynamic causal modeling (DCM) to estimate condition-dependent effective connectivity between the left anterior hippocampus (lAH) and left posterior hippocampus (lPH) from intracranial local field potential recordings obtained from subjects with simultaneous lAH and lPH coverage. We analyzed available data from two episodic memory paradigms: free recall (FR), contrasting recalled and nonrecalled items, and associative recognition (AR), contrasting correct and incorrect trials. DCMs were estimated over a 3-100 Hz frequency range, and condition-dependent coupling was summarized across three a priori frequency blocks: low-to-low coupling (3-5→3-5 Hz), low-to-theta coupling (3-5→5-10 Hz), and low-to-gamma coupling (3-5→30-70 Hz). Memory-related modulation was quantified in both anterior-to-posterior (AH→PH/B21) and posterior-to-anterior (PH→AH/B12) directions, and a directionality index was computed as AH→PH minus PH→AH to characterize task-dependent coupling patterns. Analyses revealed task dependent patterns of directed hippocampal communication associated with successful memory performance. In FR, the clearest effect was observed in posterior-to-anterior PH→AH/B12 low-to-gamma modulation, particularly in the 3-5→30-70 Hz block. In contrast, AR effects were weaker and more variable across the same frequency blocks. Formal task comparisons suggested that the FR-AR difference was driven more strongly by PH→AH/B12 modulation than by AH→PH/B21 modulation, while the directionality index followed the same pattern but was weaker. These findings suggest that successful episodic memory may engage task dependent patterns of directed cross-frequency communication along the hippocampal axis. By extending previous intracranial studies of hippocampal functional connectivity to estimates of directed effective connectivity, this work highlights the potential of induced-response DCM to distinguish shared and task specific mechanisms of hippocampal communication during memory processing.

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Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

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Program #/Poster #: PSTR378.05/KK53

Topic: I.07. Long-Term Memory

Support: Spanish National Grant PID2024-155278NA-I00

Title: Temporal Interference Stimulation of the Hippocampus and Amygdala Modulates Emotional Memory

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Abstract: Emotional memories depend on interactions between the amygdala and hippocampus (McGaugh, 2000; Costa et al., 2022, 2025). Temporal interference stimulation (TI) offers a promising approach for non-invasive modulation of deep brain structures (Grossman et al., 2017; Violante et al., 2023), yet its effects on emotional memory remain largely unexplored in humans. We tested 114 healthy participants using an emotional memory paradigm involving images from the IAPS and EmoMadrid databases. Stimulation was delivered using a Temporal Interference Solutions device through the Early Adopter Program. During encoding, participants received theta-burst-inspired TI stimulation (Wessel et al., 2023) designed to modulate medial temporal lobe activity based on previous evidence linking amygdala theta and hippocampal gamma interactions to emotional memory formation (Costa et al., 2022). Recognition memory was assessed 24 hours later and quantified using corrected recognition scores (Pr = hits − false alarms) for emotional and neutral items. A control group (n = 30) established the expected emotional memory advantage, showing enhanced memory for emotional relative to neutral stimuli. Additional participants received hippocampal-targeted TI (n = 30), low-intensity amygdala-targeted TI (n = 27), or high-intensity amygdala-targeted TI (n = 27). Hippocampal-targeted TI reduced the emotional memory advantage, primarily through increased corrected recognition for neutral information. Temporal analyses suggested that this effect emerged progressively and became more apparent during the later stages of stimulation. Amygdala-targeted TI showed an intensity-dependent profile. Low-intensity stimulation tended to preserve the emotional memory advantage, whereas high-intensity stimulation produced a pattern more similar to the hippocampal condition. Electric-field simulations suggested distinct hippocampal and amygdala-targeted field distributions. The two amygdala conditions shared a similar spatial distribution but differed in field magnitude, suggesting that intensity-dependent behavioural effects may reflect differential responses to increasing field strengths. These findings provide initial evidence that theta-burst temporal interference stimulation can modulate emotional

memory formation in a target- and intensity-dependent manner. The hippocampal findings are consistent with the proposed role of medial temporal lobe oscillatory mechanisms in emotional memory prioritization and support the potential of non-invasive deep-brain stimulation approaches for modulating maladaptive emotional-memory processes.

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Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

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Program #/Poster #: PSTR378.06/KK54

Topic: I.07. Long-Term Memory

Title: Burst-driven learning in the human medial temporal lobe

Authors: *P. CHAKRAVARTHULA[1], **S. WANG**[2];
[1]Washington Univ. Sch. of Med., Saint Louis, MO; [2]Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Neuronal bursts, defined as brief epochs of high-frequency spiking, are known to play a key role in the formation of memory engrams in rodents, where they drive synaptic plasticity more effectively than isolated spikes. However, whether burst-driven learning also occurs in humans, and the time scales at which bursts drive plasticity in humans, is not well understood. A central challenge is that human memory unfolds during active vision, as observers shift their gaze to sample visual information every 200-300 milliseconds, making it difficult to know what information a given burst encodes. To study this question, we collected simultaneous gaze and Medial Temporal Lobe (MTL) single-neuron recordings from epilepsy patients while they performed an old/new recognition task on natural scene images. We parsed burst events from the spike trains and aligned them temporally with the observer's fixations to obtain precise measurements of what information was being sampled during neuronal bursting and relate burst activity directly to memory outcomes. Our analyses revealed that: (1) bursts occur preferentially when the observer fixates novel visual information, suggesting bursting is gated by the stimulus novelty during natural viewing, (2) during encoding, bursts carve 'attractor-like' basins in the neural state space to strengthen subsequent reinstatement of the encoding neural state, (3) burst sharpen the geometry of memory representations at the population level, separating competing memories and enhancing stored pattern retrieval. Further, a burst-gated Modern Hopfield Network reproduces these dynamics, recapitulating recognition behavior and revealing burst-gating as a sufficient computational mechanism for memory storage and retrieval. Taken together, these results suggest that bursts act as a fixation time-scale plasticity mechanism that supports one-shot learning of complex visual content during natural visual exploration and point to burst-gated plasticity as a unifying principle linking rodent and human memory research.

Disclosures: P. Chakravarthula: None. **S. Wang:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR378.07/KK55

Topic: I.07. Long-Term Memory

Support: NINDS 1R01NS107357-03
NINDS 1R01NS125250
Wilson Foundation

Title: Hippocampal Barques Are Associated With Enhanced SO-Spindle-Ripple Coupling During NREM Sleep

Authors: *D. CHAKRAVARTY[1], B. C. LEGA[2];
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Abstract: The hippocampal barque is a recently characterized intracranial EEG burst oscillation of 0.5-2 seconds at 14 Hz, 6 Hz, or a 14/6 Hz overlap, arising predominantly in the posterior hippocampus in 30% of patients. These events appear with equal prevalence in epileptogenic and non-epileptogenic hippocampi and occur almost exclusively during NREM stage II and slow-wave sleep. This timing is notable because memory consolidation occurs similarly during NREM sleep and is thought to depend on the coordinated coupling of slow oscillations (SOs), sleep spindles, and hippocampal sharp-wave ripples, in which ripples are nested in spindle troughs that are grouped by SO up-states. The temporal and anatomical overlap between barques and this coupling cascade raises the question of whether barque-positive hippocampi show altered organization of sleep-related coupling. We analyzed overnight intracranial EEG from 29 epilepsy patients selected for analysis: 15 with barques and 14 without. SOs, spindles, and ripples were detected from bipolar hippocampal contacts, and group differences were tested with electrode-level linear mixed effects models. NREM sleep segments were computationally scored on iEEG by two methods (Geva-Sagiv et al., 2023; SleepSEEG, von Ellenrieder et al., 2022). Three convergent findings emerged in the posterior hippocampus. The fraction of NREM ripples co-occurring with spindles was greater in barque-positive patients compared to barque-negative patients (0.30 vs 0.19; $p=2.9\times10^{-5}$), with this relationship holding after adding spindle count as a covariate ($p=4.2\times10^{-5}$). Spindle-ripple phase-amplitude coupling was also elevated in Barque-positive patients (MVL 0.016 vs 0.010, p=0.015; confirmed by modulation index, p=0.044), indicating that ripples were more precisely timed within the spindle cycle. Complete SO-spindle-ripple cascade events occurred at a higher rate in Barque-positive patients (18.9 vs 14.2/hr, p=0.030), with no group difference in SO density or amplitude. Each finding was reproduced under both sleep scoring methods. These results demonstrate that the SO-spindle-ripple cascade is more tightly organized in barque-positive than barque-negative hippocampi, with this effect

regionally specific to the posterior hippocampus where barques predominate. Taken together, these findings suggest that barque-positive hippocampi exhibit a distinct profile of enhanced coupling, consistent with the idea that the neural physiology underlying barque generation also supports a more coordinated hippocampal sleep architecture relevant to memory consolidation.

Disclosures: D. Chakravarty: None. **B.C. Lega:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

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Program #/Poster #: PSTR378.08/KK56

Topic: I.07. Long-Term Memory

Support: ERC2019-COG 866093

Title: A single brief reactivation of memory enhances long-term retention

Authors: *R. PHILOS[1], S. KOZAK[2], O. DEZACHYO[1], G. SCHRIFT[1], N. CENSOR[2,1]; [1]Sagol Sch. of Neurosci., [2]Sch. of Psychological Sci., Tel Aviv Univ., Tel Aviv, Israel

Abstract: Following their reactivation, consolidated memories may become susceptible to modification (Misanin et al., 1968; Nader et al., 2000). However, the impact of memory reactivation on long-term memory stability remains unclear. To address this question, we leveraged a novel memory reactivation paradigm enabling to map the effects of memory reactivation on long-term temporal dynamics of episodic memory retention (n=21). The results show that a single brief exposure to a visual cue reactivating the memory is sufficient to enhance memory retention over time. Reactivated memories were better retained than non-reactivated memories one month following reactivation ($t_{20}=2.44$, $p=0.024$), suggesting that reactivation serves as a long-term stabilizing mechanism of episodic memory. When reactivation was followed by an immediate memory test (n=20), its long-term beneficial effect on memory was abolished ($t_{19}=1.1$, $p=0.283$), implicating time-dependent reactivation-reconsolidation mechanisms. These results indicate that an isolated brief reactivation promotes long-term episodic memory retention, suggesting a link to time-dependent consolidation and reorganization processes of memory-related brain regions.

Disclosures: R. Philos: None. **S. Kozak:** None. **O. Dezachyo:** None. **G. Schrift:** None. **N. Censor:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR378.09/Web Only

Topic: I.07. Long-Term Memory

Support: Canada Research Chairs Program (950- 233046)
CIHR Institute of Cancer Research – Breast Cancer Survivorship Priority Announcement grant to MJS
Ontario Graduate Scholarship (OGS)

Title: Investigating Memory-Related Brain Structures in Chemotherapy-Treated Breast Cancer Survivors Using the CentileBrain Normative Deviation Framework

Authors: *N. ELMAWAZINI[1], K. D. MUNELITH-SOUKSANH[1], I. X. MACPHEE[2], J. A. ANDERSON[3], M. J. SEKERES[1];
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Abstract: Breast cancer survivors who undergo chemotherapy frequently report cognitive difficulties, often described as "brain fog," including mental fatigue and memory impairment. Neuroimaging studies have identified structural brain alterations following chemotherapy, however, findings remain mixed and may be limited by reliance on traditional group comparison approaches. The present study used CentileBrain, a normative modelling framework based on approximately 17,000 healthy individuals, to determine whether breast cancer survivors exhibit deviations from expected brain morphology. We assessed three structural parameters: subcortical volumes, cortical thickness, surface area. Structural magnetic resonance imaging data were collected from 25 women aged 30 to 65 years who had completed chemotherapy for breast cancer and 38 healthy controls. CentileBrain generated z-scores for brain regions based on age and sex. One-sample t-tests assessed whether breast cancer survivors significantly deviated from the normative population mean, and independent-samples t-tests were used to compare the deviation of survivors with healthy controls. Breast cancer survivors showed a significant deviation from normative expectations in the left rostral middle frontal surface area, with increased values relative to the normative mean ($p = 0.004$). For this analysis, we were also particularly interested in investigating the hippocampus because chemobrain has been associated with long-term memory impairment and hippocampal alterations. However, our analyses revealed that hippocampal and parahippocampal measures in chemotherapy-treated breast cancer patients did not differ significantly from normative values and healthy controls. These findings provide evidence of region-specific structural deviations following chemotherapy, particularly within frontal regions implicated in executive functioning. By leveraging large-scale normative modelling, CentileBrain increases sensitivity to subtle structural variation and supports the interpretation that observed alterations may reflect meaningful departures from expected brain morphology. This work advances understanding of the neural correlates of cancer-related cognitive impairment and highlights the value of normative neuroimaging approaches for detecting chemotherapy-associated brain changes.

Disclosures: N. Elmawazini: None. **K.D. Munelith-Souksanh:** None. **I.X. MacPhee:** None. **J.A. Anderson:** None. **M.J. Sekeres:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR378.10/KK58

Topic: I.07. Long-Term Memory

Support: Mitacs Globalink Research Award FR121655
New Frontiers Research Fund NFRFE-2019-508778
Canada Foundation for Innovation 35923
Max Planck-University of Toronto Centre for Neural Science and Technology
Max Planck Society

Title: Multi-scale neural coding of visuospatial memory in the human brain

Authors: *Q. CHU[1,2,3], T. M. BIBA[2,3], I. SKELIN[4,3], X. XIAO[2,3,5], A. CORNEJO MARIN[3], T. A. VALIANTE[2,3], L. MELLONI[1,4,6];
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Abstract: Item-location binding, in which object identity ("what") is associated with spatial context ("where") to support later recollection, is central to episodic memory. Yet the neural mechanisms for forming item-location memory remain incompletely understood. In prior work, we identified two distinct neuronal populations: item neurons in the medial temporal lobe (MTL) and gaze-location neurons confined to the parahippocampal cortex (Chu et al., 2026). This disjunctive item-context coding departs from conjunctive schemes reported in other species and is consistent with proposals that human memory representations flexibly orthogonalize items and contexts (Quiroga, 2019). How these dissociable codes are bound into individual episodes however remains unknown. Here, we test two candidate neural mechanisms for item-location binding using intracranial recordings from 15 individuals with epilepsy performing a visuospatial memory task. First, we examined an episode-indexing mechanism in which episode-specific neurons (ESNs) conjunctively tag individual experiences without tuning to any single memory element (Kolibius et al., 2023, 2025). We hypothesized that visuospatial ESNs would increase firing during both encoding and retrieval of the same item-location episode, while showing no selectivity for any individual item or location. Using the method of Kolibius et al. (2023) with additional false discovery rate control, we identified a significant proportion of putative ESNs in the MTL (23/284 neurons, 8.1%; $P < 0.001$). ESNs exhibited relatively low firing rates yet high selectivity, with significant reinstatement for no more than three of ~100 encoding-retrieval pairs per neuron. These findings provide some support for ESNs in a visuospatial memory task and suggest that the human MTL may implement an index-like code to individuate episodes. Second, building on our prior observation that gaze-location neurons were restricted to the parahippocampal cortex, we tested whether location might instead be represented by multivariate oscillatory signals in the MTL and frontoparietal cortices. We aggregated electrodes across participants and applied RSA and decoding to broadband iEEG (1-150 Hz). Preliminary analyses

revealed significant gaze-location patterns across multiple regions, although potential contributions from oculomuscular artifacts in iEEG complicate interpretation. Together, these results suggest that, beyond single neurons tuned to item and context elements, complementary mechanisms such as episode indexing and oscillatory population codes may support the formation of item-location memories.

Disclosures: Q. Chu: None. **T.M. Biba:** None. **I. Skelin:** None. **X. Xiao:** None. **A. Cornejo Marin:** None. **T.A. Valiante:** None. **L. Melloni:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR378.11/KK59

Topic: I.07. Long-Term Memory

Support: NIH MSTP T32 Training Grant (T32GM144300)
NIH R01 MH132225
NIH P50 MH109429

Title: Macroscale cortical states predict fluctuations of mesoscale hippocampal sharp wave-ripples and single-neuron firing at a minutes timescale

Authors: *D. GENG[1], M. B. WANG[2], A. ALREJA[3], M. J. WARD[4], J. J. LIN[5], J. CASTELLANO[6], T. J. ABEL[7], A. BARI[4], R. E. KASS[9], A. S. GHUMAN[8];
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Abstract: While empirical studies and biophysical modeling have linked moment-to-moment microscale, single-unit firing, mesoscale local field potential features, and macroscale global brain state, little is known about how these spatial scales relate across temporal timescales. Here, we examine the temporal relationship between large-scale, global brain states, mesoscale hippocampal sharp wave ripples (SWRs), and microscale single units using continuous, multi-day intracranial EEG from eight epilepsy monitoring unit patients (5-7 days). SWRs were chosen as mesoscale features because they are brief, high-frequency oscillatory events that have been mechanistically characterized as spatially localized, mesoscale phenomena. The global cortical state was defined as the pattern of oscillatory and aperiodic spectral features across cortical regions. We systematically characterized whether this global cortical state can predict these hippocampal SWR and single unit firing fluctuations from the hippocampus, and if so, what features, spatial organization, and timescales characterize this relationship. Cross-day validated

analyses demonstrated that the cortical state predicts SWR occurrence ($p < 0.001$, 8/8 patients), persisting after slow-drift detrending and when restricted to NREM sleep. Feature-type ablation revealed that the aperiodic offset (reflecting broadband activation levels), rather than the oscillatory band powers, dominated prediction. Anatomical ablation analyses demonstrated the signal is distributed spatially across cortical regions rather than localized. Koopman operator theory and temporal lag analyses independently converged on a predictive timescale of minutes (predicting SWR modulation minutes ahead of time), with signal persisting across extended lags. Taken together, these reveal a distributed cortical state, dominated by aperiodic offset, which operates at a minutes timescale. To extend our findings across spatial scales, we additionally tested whether the same cortical features predict hippocampal single-neuron firing in a patient with depth microelectrodes and rigorous spike sorting, and found that the macro-to-micro relationship matched the macro-to-meso pattern across feature identity, dynamical timescale (predicting firing rate minutes ahead), and temporal persistence. These findings point to a key timescale for neural organization - a minutes-timescale distributed cortical state that shapes hippocampal activity from population-level ripples to individual neuron firing, and may reflect a principle governing how temporal dynamics propagate across spatial scales.

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Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR378.12/KK60

Topic: I.07. Long-Term Memory

Support: NIH R56 AG058685
NIH R01 AG040133
NSF BCS-2234398

Title: Neural population trajectories across wake and sleep support memory consolidation

Authors: *T. NG[1,2], R. ZAID[3], L. KAMKAR[4], M. BARNES[6], I. ORLOVSKY[7], L. MOONEY[4], R. M. C. SPENCER[5];
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Abstract: Memory consolidation transforms learning-induced population states into stable representations, yet encoding, consolidation, and retrieval are mostly studied in isolation. We tested whether memory is better explained as a cross-state trajectory using three high-density EEG datasets: 1) word-pair learning across sleep/wake/pseudoword nights (N=35), 2) emotional

recognition across nap/wake intervals in young and older adults (N=30), and 3) slow oscillation (SO) up/down-state phase-locked acoustic targeted memory reactivation (TMR) in NREM following a spatial task (N=20) with face/object/scene image-sound pairs recalled before/after a nap. We quantified continuous aperiodic 1/f trajectories indexing broadband cortical excitability and trial-level sleep SO-spindle and wake theta-alpha wave propagation trajectories, using these spatiotemporal features to decode representations across encoding, sleep cueing, and retrieval, with label, cue-time, and phase surrogate controls. Sleep preserved verbal and recognition memory relative to wake (*ps*<0.01). Supporting a cross-state framework, learning flattened pre-sleep wake 1/f slopes relative to sham ($p<0.001$) but steepened NREM slopes ($p=0.002$; wake-sleep contrast $p=0.020$); regions with the strongest wake distortion showed the strongest sleep realignment ($r=0.59$, $p<0.001$), resolving the wake-induced plasticity burden. This contrast predicted memory stabilization ($r=0.44$, $p=0.003$) better than single-state measures. Revealing how this state-level trajectory is routed across the cortex, sleep and wake traveling waves at the network level exhibited more precise cross-frequency coupling phase/strength than local events (*ps*<0.027), and their across-trial directional consistency predicted recall ($r=0.64$, $p=0.002$). Phase-locked perturbation of this propagation regime showed that up-state TMR cues improved spatial memory precision ($p=0.034$), with greater benefit after repeated cueing ($p=0.008$), and triggered subsequent SO-spindle traveling wave cycles ($p<0.001$), whose increase predicted lower post-sleep error ($p=0.027$). Phase-gradient decoding then mapped representational routing along this trajectory: same-item and same-category similarities were significant from encoding-to-sleep (category $p=0.006$; item $p=0.036$) and sleep-to-retrieval (category $p=0.008$; item $p=0.038$), but not direct encoding-to-retrieval or down-cued/shuffled controls, indicating that routing did not bypass sleep. Localizer controls ruled out image/sound-driven similarity. This cross-level evidence supports wake-sleep trajectories as a mechanism for memory reorganization.

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Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

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Program #/Poster #: PSTR378.13/KK61

Topic: I.07. Long-Term Memory

Support: R01MH128552
T90DA059109

Title: Self-directed learning shapes hippocampal memory rhythms in humans

Authors: *K. ROSTOWSKY, J. E. KRAGEL, J. L. VOSS;
Neurol., Univ. of Chicago, Chicago, IL

Abstract: Memory is often better following learning that occurs with control over where and when to study, versus with passive receipt of the same information. One possible explanation for these effects is that self-directed learning is beneficial because it involves control of exploratory behaviors, such as eye movements, which are known to engage memory-related theta rhythms in the hippocampus. To test whether the influence of exploratory eye movements on hippocampal activity explains benefits of self-directed learning, we used intracranial encephalography (iEEG) to record hippocampal activity from human patients (N=3) while they performed a novel gaze-contingent episodic memory task. Specifically, we compared hippocampal iEEG between self-directed eye movements and those made in a matched passive condition to isolate signals related to volitional control. During a trial, a set of crosses appeared at random non-overlapping locations on a computer screen. Each cross concealed a hidden object which could be revealed by looking at its center. Patients were instructed to memorize the identity and location of each hidden object. In a self-directed "Active" condition, patients could choose which crosses to look at and when. In a "Passive" condition, patients were instructed to look at crosses as they were cued, with the order yoked to that of other patients' Active condition. In this preliminary dataset, recognition memory was higher in the Active than the Passive condition (paired t-test, $p=0.0065$). To identify neural correlates of self-directed learning in the hippocampus, we focused analyses on theta rhythms (3-8Hz) recorded via depth electrodes in the right (N=10) and left (N=6) hippocampus. Preliminary analyses revealed hippocampal theta pairwise phase consistency (PPC) following a saccade was greater for the Active than the Passive condition (Wilcoxon signed-rank test, $p=0.023$). 75% of contacts exhibited greater PPC during the Active condition. Subsequent one-sided permutation testing revealed significantly greater PPC in 6 of 16 contacts in the Active condition (N=1000 iterations, $p<0.05$). These findings indicate stronger alignment of hippocampal theta rhythms following saccades made during self-directed learning and offer a novel insight into how control over learning can shape memory-related hippocampal rhythms. Ongoing analyses will examine if PPC is related to memory performance and characterize if self-directed learning supports differential aspects of memory (e.g. recognition and spatial memory). Our preliminary findings suggest a complex interplay between exploration and self-directed learning that supports hippocampal processes.

Disclosures: K. Rostowsky: None. **J.E. Kragel:** None. **J.L. Voss:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR378.14/KK62

Topic: I.07. Long-Term Memory

Support: R01MH128552

Title: Effects of gaze-locked stimulation on viewing behavior during scene recognition

Authors: *P. SHARMA[1], J. E. KRAGEL[2], J. L. VOSS[1];
[2]Neurol., [1]Univ. of Chicago, Chicago, IL

Abstract: Where we look while viewing a scene shapes what we remember. During visual exploration of naturalistic scenes, a minority of fixations called “revisits” occur when the gaze returns to a previously viewed location rather than sampling novel content. Revisits predict reinstatement of scanpaths during retrieval, thereby serving as an indicator of spatiotemporal memory encoding. They have also been associated with modulations in hippocampal theta oscillations relative to novel fixations, which may provide a neural correlate of the impact of revisit fixations on memory encoding. Yet, these relationships remain correlational. Here, we used high-frequency direct electrical stimulation to transiently disrupt hippocampal activity and directly test whether the hippocampus causally contributes to the memory effects associated with revisit fixations. Patients undergoing intracranial EEG for presurgical epilepsy monitoring performed a continuous recognition task for naturalistic scenes. We delivered 100-200 ms of 50 Hz stimulation directly to the hippocampus (n=6). Eye tracking was used to synchronize stimulation during scene encoding to either (1) revisit fixations or (2) other fixations to novel locations. We further compared the effects of revisit-locked stimulation to (3) control stimulation not locked to eye fixations, and (4) a baseline without stimulation. Recognition accuracy did not differ among any stimulation conditions (all $p > 0.1$). However, eye movements associated with memory varied by stimulation condition. In subjects receiving hippocampal stimulation locked to revisit fixations, correctly recognized trials had more fixations during encoding relative to retrieval compared to forgotten trials ($p=0.009$). This modulation of eye movements by memory status did not occur for hippocampal stimulation locked to novel fixations ($p=0.389$) or at baseline ($p=0.182$), and occurred less robustly for control stimulation ($p=0.044$). This demonstrates that the hippocampus participates in the guidance of eye movements during encoding, particularly at moments when revisit fixations occur. Increased sampling during encoding may represent a compensatory strategy to offset stimulation-induced encoding deficits. Findings from a group of subjects who received stimulation of the lateral temporal cortex as a control location will also be discussed.

Disclosures: P. Sharma: None. **J.E. Kragel:** None. **J.L. Voss:** None.

Poster

PSTR378: Long-Term Memory in Human Medial Temporal Lobe

Location: WCC Halls A-C

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Program #/Poster #: PSTR378.15/KK63

Topic: I.07. Long-Term Memory

Support: Israel Science Foundation 526/17
Israel Science Foundation 1298/23

Title: Neuromodulation of reactivated traumatic memories: hippocampal-network-targeted TMS as a novel PTSD intervention

Authors: *O. DEZACHYO[1], N. YAIR[2,3], R. PHILOS[1,3], N. TIK[2], H. SHARON[4], D. S. PINE[5], I. TAVOR[2,1], Y. BAR-HAIM[3,1], N. CENSOR[1,3];
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Abstract: Intrusive traumatic memories are a core symptom of posttraumatic stress disorder (PTSD). The hippocampus plays a central role in their storage, however, its deep location limits direct access by non-invasive neuromodulation. Here, we introduce a novel non-invasive treatment for PTSD, leveraging hippocampal-network-targeted repetitive transcranial magnetic stimulation (HNT-rTMS) delivered immediately following traumatic memory reactivation. Accordingly, resting-state functional magnetic resonance imaging (rs-fMRI) is used to identify parietal cortical nodes accessible with TMS, having strong functional connectivity (FC) with the hippocampal target. We initiated a double-blind randomized control trial (RCT) to systematically evaluate efficacy. Participants are randomized to receive five weeks of identical inhibitory HNT-rTMS, targeted either at the personalized hippocampal network or an out-of-network cortical control site. Clinical outcomes are assessed at a 3-month follow-up to evaluate long-term symptom trajectories. In an initial open trial (N =10), five weekly sessions of personalized, fMRI-guided inhibitory HNT-rTMS post-memory reactivation proved safe and well-tolerated. Resting-state fMRI confirmed reduced functional connectivity within the hippocampal network ($t(9) = -2.97$, $p < 0.01$), accompanied by significant clinical reductions in daily trauma intrusion and overall PTSD symptom severity ($t(9) = 4.38$, $p < 0.001$). We report that 40 subjects have completed the RCT protocol to date, demonstrating safety and tolerability profiles consistent with the initial open trial. These lines of work are expected to open the door for novel interventions geared to alleviate hippocampal-dependent memory disorders such as PTSD.

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Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR379.01/KK64

Topic: I.08. Learning and Memory

Support: NIH grant ZIA MH002928
Brain and Behavior Foundation Grant 32825

Title: Embodied reinforcement learning in primates

Authors: *F. GIARROCCO[1], B. B. AVERBECK[2];
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Abstract: Learning the value of environmental stimuli from reward experience allows animals to make advantageous choices. Existing biological accounts of reinforcement learning (RL) often assume that this value is represented as a single, motor-system-invariant neural signal. We tested this assumption by recording across eight nodes of the macaque cortico-basal ganglia system — from limbic to neocortical regions — while monkeys learned stimulus-reward associations using either saccades or reaches as the required motor response. The geometry of population activity revealed largely distinct value-coding dimensions for saccades and reaches, including in limbic regions typically associated with motor-system-invariant value coding. Consequently, value information was substantially reduced when read out across motor systems. These results provide circuit-wide evidence that challenges existing neural implementations of RL. They link biological accounts of value learning to embodied frameworks across cognitive science and artificial intelligence, in which behavior is grounded in an agent's physical structure rather than abstracted from it.

Disclosures: F. Giarrocco: None. **B.B. Averbeck:** None.

Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR379.02/KK65

Topic: I.08. Learning and Memory

Support: ZIA MH002928

Title: The neurobiological underpinnings of MRI-derived cortical thickness changes across adolescence

Authors: *M. AUSTIN[1], M. ANDUJAR[2], B. AVERBECK[1];
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Abstract: The neurobiological underpinnings of MRI-derived cortical thickness changes across adolescence By: Mikhyah Austin, Marta Andujar, Bruno Averbeck
Cortical thinning during development has been well-documented. It is the observed reduction in cortical grey matter, estimated from T1-weighted MRI images, over the course of adolescence and into adulthood. Deviation in gray matter volume from its typical trajectory during development is observed in many psychiatric conditions. Understanding the neurobiological underpinnings of this developmental phenomenon may uncover important clinical implications. The apparent reduction in gray matter has been observed to follow a hierarchical developmental pattern, in which primary sensory and motor areas peak in early adolescence, followed by transmodal and associative areas that continue to mature well into adulthood. This is known as the sensorimotor-to-association (S-A) axis. Interestingly, this same hierarchical pattern has been observed in the development of myelin, with increases in myelin content occurring first in sensorimotor areas, followed by association areas. This parallel pattern of development raises the

question of whether this MRI-estimated thinning of gray matter could be driven by a shift in the gray/white matter boundary propagated by progressive myelination of intracortical fibers? To address these questions, we acquired structural MRIs from 12 rhesus macaques spanning 2 to 12 years of age. From this, we derived cortical thickness estimates from T1-weighted images and intracortical myelin content from the T1w/T2w ratio. Parcels of the CHARM atlas were classified along the S-A axis to characterize developmental trajectories of both measures across the cortical hierarchy. We further validate these in vivo findings with myelin-stained coronal sections from the same subjects, sampling four cytoarchitectonically distinct prefrontal subdivisions: granular dorsolateral cortex (Broadman areas 9 and 46), frontopolar cortex (area 10), pregenual cingulate cortex (area 32), and ventromedial orbital cortex (area 14). By directly measuring the depth-dependent progression of myelin into the cortical ribbon, this histological validation allows us to test the proposed neurobiological mechanism — whether deep-layer myelination is sufficient to account for the MRI-estimated thinning — across regions that span the eulaminate-to-agranular gradient of prefrontal organization.

Disclosures: M. Austin: None. **M. Andujar:** None. **B. Averbeck:** None.

Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR379.03/LL1

Topic: I.08. Learning and Memory

Support: ZIA MH002928

Title: Multimodal mapping of adolescent cortico-striatal maturation in the primate brain

Authors: *M. ANDUJAR[1], B. B. AVERBECK[2];
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Abstract: Adolescence is a conserved developmental transition bridging puberty and adulthood, characterized by profound behavioral and neural remodeling. However, how this remodeling proceeds across cortico-striatal circuits during primate adolescence, and what behavioral consequences it carries, remains poorly characterized. To address these questions, we conducted a multimodal investigation of adolescent brain development in macaques, integrating reinforcement learning-based behavioral modeling and ex vivo cellular and physiological analyses. Behavioral results reveal that juvenile monkeys show reduced learning from positive feedback compared to late adolescents, consistent with less accurate value representations. To identify the neural substrates underlying these behavioral differences, we examined synaptic pruning across prefrontal cortex and found region-specific trajectories, with eulaminate area 46 and limbic area 25 following distinct developmental profiles. Interestingly, this structural remodeling was accompanied by region-specific physiological maturation: pyramidal neurons in area 46, but not area 25, increased their firing rates, while excitatory postsynaptic events showed

faster rise and decay kinetics — consistent with a redistribution of synaptic inputs along the dendritic tree and reduced cable filtering. To probe downstream targets of these prefrontal changes, we next examined the dorsal striatum using the same cellular approach combined with fast-scan cyclic voltammetry. Synaptic density was preserved across adolescence, whereas dopamine availability increased markedly. Together, these findings reveal that adolescent maturation of cortico-striatal circuits in primates proceeds through region- and modality-specific trajectories, with structural and functional refinement in prefrontal cortex paralleled by a neuromodulatory rebalancing in the striatum. This configuration may bias adolescent reinforcement learning toward positive feedback and provide a circuit-level framework for understanding the heightened psychiatric vulnerability of this developmental window.

Disclosures: M. Andujar: None. **B.B. Averbeck:** None.

Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

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Program #/Poster #: PSTR379.04/LL2

Topic: I.08. Learning and Memory

Support: ZIA MH002928

Title: Adolescence amplifies positive feedback learning in rhesus macaques

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Abstract: Adolescence is a developmental period characterized by distinctive changes in reward-guided behavior, including shifts in sensitivity to feedback, exploration, and learning from outcomes. Reinforcement learning (RL) models provide a principled framework for parsing these changes into separable components — learning rate, valence asymmetry, and choice stochasticity. Developmental RL studies have focused largely on adolescent humans, with findings suggesting age-related modulation of these processes. Non-human primate models offer a complementary approach, enabling dense within-subject sampling across multiple reward environments and direct access to the neural substrates that mature during adolescence. We tested rhesus macaques at three developmental stages — juvenile (2-year-old, N = 4), late adolescent (5-year-old, N = 4), and adult (12-year-old, N = 1) — on a two-arm bandit task under deterministic (100/0) and stochastic (80/20) reward schedules. Among five RL models, an asymmetric Rescorla-Wagner model with separate learning rates for positive (αPos) and negative (αNeg) prediction errors best captured choice behavior across all groups and conditions. Positive learning rate followed a non-monotonic developmental trajectory peaking in adolescence: late adolescent monkeys showed significantly higher αPos than juveniles and adults. The adolescent peak in αPos was reflected in faster behavioral learning curves under deterministic reward, but not under stochastic reward. Under stochastic conditions, a higher

learning rate produces both faster uptake of valid information and stronger reactions to occasional noisy outcomes, with these opposing effects offsetting each other at the group-behavioral level. These findings identify a transient peak in value-based learning rate during adolescence in rhesus macaques. This behavioral signature provides a quantitative entry point for future investigations of its neural underpinnings — in particular, the protracted maturation of dopaminergic prefrontostriatal circuits, whose remodeling during adolescence has been linked to changes in reward processing and synaptic plasticity in this developmental window.

Disclosures: T.M. Annnulis: None. **M. Andujar:** None. **B.B. Averbeck:** None.

Poster

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Support: Brain Science and Brain-like Intelligence Technology -National Science and Technology Major Project under Grant 2021ZD0204300
NARSAD Young Investigator Grant 30892

Title: Task-dependent reconfiguration of critical dynamics in macaque lateral prefrontal cortex

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Abstract: Cortical circuits must balance flexibility for rapid processing of incoming information with stability to maintain task-relevant activity once an action plan is selected. Operation near criticality has been proposed to optimize this balance by placing networks in a scale-free dynamical regime characterized by high sensitivity and efficient information propagation. While recent evidence shows that cortical networks can be homeostatically tuned toward criticality, it remains unclear whether critical dynamics are present in primate association cortex and whether this state is rapidly reconfigured by shifting cognitive demands. To address this question, we recorded neural activity from the bilateral lateral prefrontal cortex (LPFC) of macaques performing a visually guided saccade task. Each trial consisted of an inter-trial interval, a fixation, a cue, and a reward period. We characterized criticality as scale-free population dynamics at two complementary levels: the spatiotemporal propagation of neuronal avalanches and the large-scale topology of event-synchronized functional assemblies. Within avalanche dynamics, we quantified deviations from the criticality coefficient (DCC) and the branching ratio. For the functional network architecture, we evaluated the goodness-of-fit and the exponent of power-law relationships among neuronal assemblies. We found that during the fixation period, the scale-free functional architecture of LPFC peaked in strength as its branching dynamics

approached a critical regime. This unique configuration established a critical, initialization-like state that optimizes the balance between stability, maintaining robust task readiness, and flexibility, thereby priming the network to process incoming sensory cues and rapidly transition into appropriate actions. Following cue onset, LPFC dynamics departed from this near-critical preparatory regime, exhibiting increased DCC, decreased scale-free goodness-of-fit, an elevated branching ratio, and a shallower power-law exponent. This directional shift suggests a transition from a flexible preparatory state into a more constrained, task-specific attractor-like regime that stabilizes the selected saccade plan and minimizes vulnerability to competing perturbations. Finally, during reward processing, the functional assembly organization reorganized to reset the network for the subsequent trial. Together, these results demonstrate that the LPFC leverages near-criticality as a flexible preparatory set point during attentive fixation, then dynamically shifts away from this regime to stabilize task-specific action execution.

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Poster

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Program #/Poster #: PSTR379.06/LL4

Topic: I.08. Learning and Memory

Support: ZIA-MH002928(BA)

Title: Coordinated limbic dynamics predict motivational engagement and disengagement

Authors: *D. BURK, B. B. AVERBECK;
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Abstract: Whether an animal engages in a behavior is a fundamental but poorly understood problem. Motivational disengagement is widely attributed to low expected reward, yet animals repeatedly disengage even when reward expectations are constant, suggesting a latent mechanism beyond value. We trained two rhesus macaques on a token-based reinforcement learning task that dissociated immediate reward from motivation. Despite the task requiring monkeys to repeat an aborted trial until completed, the monkeys entered sequences of aborted trials that revealed slow fluctuations in engagement over multiple trials. We conducted simultaneous neural recordings across the limbic system in the Ventral Striatum (VS), Ventral Pallidum (VP), Lateral Hypothalamus (LH), Insula (Ins), and Amygdala (Amyg), yielding 7759 units across 69 recording sessions. Model-derived estimates of state value, which reflect immediate and future expected rewards, were higher before continued engagement and lower before abort sequences, indicating that higher state value was associated with sustained engagement. However, state value remained constant across consecutive aborts, leaving the sequential structure of disengagement unexplained by reward alone. Population activity in all

five limbic areas during the intertrial interval (ITI) predicted upcoming trial engagement (complete or abort) before behavioral onset. At the onset of disengagement, neural activity was displaced from the engaged population state, and the number of areas displaced predicted whether disengagement would persist, indicating a network-level signal rather than parallel single-area effects. During disengagement, inter-area correlations increased and population variance concentrated onto a shared low-dimensional axis. Further analysis of the ITI dynamics revealed attractor basins for engaged and disengaged states. The depths of these basins were modulated by state value, providing a mechanism by which value modulates, but does not determine, motivational state. These findings show that motivational state is carried in the coordinated dynamics of the limbic circuit and provide insight into how disruptions in these processes may contribute to apathy and anergia in psychiatric disease.

Disclosures: D. Burk: None. **B.B. Averbeck:** None.

Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

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Topic: I.08. Learning and Memory

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Title: Sleep-Inspired Replay Enables Continual Learning via Representation Sparsification

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Abstract: One of the central challenges in artificial neural networks is continual learning: acquiring new tasks without degrading performance on previously learned ones - a phenomenon known as catastrophic forgetting. While several algorithms have been proposed to address this, they are typically applied during or immediately after each new episode of training. In contrast, the human brain learns continuously, acquiring multiple tasks before an episode of sleep consolidates them into long-term storage. Here we show that a single unsupervised sleep phase, applied after sequential training on multiple tasks in an artificial neural network (ANN), can substantially restore performance across all previously learned tasks. We implement sleep as a fully unsupervised phase incorporating stochastic network activation with local Hebbian learning rules - requiring no additional data and applicable to pre-trained models - and apply it to feedforward networks trained sequentially across MNIST, Fashion-MNIST, and CIFAR-10 benchmarks. We show that sleep-like replay downscales synaptic weights broadly while selectively strengthening only a small subset of critical synapses, increasing the sparseness of neuronal representations and reducing the number of active neurons. This sparsification

orthogonalizes task representations, minimizing inter-task interference and enhancing memory retention across all tasks. Importantly, task-specific information remains resilient to new training but decays gradually as the network is exposed to additional tasks, suggesting a finite consolidation window that sleep replay can exploit. Our study suggests that this sleep-induced sparse representation - fewer active neurons encoding more separated task representations - plays a central role in continual learning, pointing to novel principles for developing continual learning AI solutions.

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Poster

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Topic: I.08. Learning and Memory

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Title: Noradrenergic control of cortical up-state window for NREM sleep rhythm coordination in a biophysical model of the cortico-thalamo-hippocampal loop

Authors: *M. WEI[1], R. GOLDEN[2], W. GOCH[3], G. P. KRISHNAN[4], O. ESCHENKO[5], P. SANDA[6], M. V. BAZHENOV[7];
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Abstract: Sleep plays a key role in brain function, including memory consolidation, yet the mechanisms by which neuromodulatory systems regulate memory-related brain activity during sleep remain poorly understood. During non-rapid eye movement (NREM) sleep, cortical up-states, the active phase of the sleep slow oscillation (SO), provide a critical temporal window for coordinating thalamocortical spindles, hippocampal ripples, and hippocampal-cortical replay to support memory consolidation. The duration of this window has been shown to play an important role in the outcome of memory consolidation, with longer up-states promoting reactivation of familiar cortical memories. While the locus coeruleus-norepinephrine (LC-NE) system is traditionally associated with wakefulness and arousal, recent evidence indicates that LC activity is dynamically structured during NREM sleep and may regulate this up-state-centered coupling window. Here, we tested whether LC-NE modulation of cortical excitability

controls up-state duration in a large-scale biophysical model of the cortico-thalamo-hippocampal loop.During NREM sleep, LC neurons exhibit rhythmic population bursting, which drives corresponding infraslow (~0.05 Hz) fluctuations in extracellular NE levels. Because burst-evoked NE peaks can recruit low-affinity β-adrenergic receptors, we modeled the cortical β-adrenergic effect of LC burst-evoked NE as suppression of the effective calcium-activated potassium afterhyperpolarization conductance (G_KCa) in cortical pyramidal neurons and examined how this modulation alters cortical up-states. We then varied the magnitude of this β-adrenergic modulation and quantified its effect on up-state duration. Stronger LC-NE-mediated suppression of G_KCa prolonged up-states, whereas reducing this suppression preserved more KCa-mediated hyperpolarizing currents and shortened up-states. In parallel experimental analysis, cortical gamma events, defined by elevated 30-40 Hz EEG power, were temporally linked to LC bursts. Because these gamma events mark a subset of multiunit-activity-defined cortical up-states, gamma event duration provided an experimental readout of up-state-associated cortical activation. Longer delays from LC burst to gamma onset predicted shorter gamma event duration, consistent with a transient LC-dependent window of prolonged up-states. Together, the model and data support a mechanism in which precisely timed LC-NE signaling shapes NREM network dynamics, potentially influencing the outcome of memory consolidation.

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Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

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Topic: I.08. Learning and Memory

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NIH Grant 1R01AG099626

Title: Sleep to forget: active control of consolidation and forgetting by slow-wave sleep dynamics

Authors: *R. GOLDEN[1], M. WEI[2], S. COURY[3], A. MIZRAHI-KLIGER[3], K. GANGULY[4], M. V. BAZHENOV[5];
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Abstract: Sleep promotes memory consolidation through coordinated interactions between cortical slow-wave activity and memory replay. It is generally assumed that consolidation is a process of forming stable long-term memory representations. Although cortical replay occurs throughout slow-wave sleep (SWS), studies have not typically differentiated between slow

oscillation (SO; <1 Hz) and delta wave (δ; 2-4 Hz) activity. Recent experimental work suggests that SO and δ events have opposing effects on memory, with SO strengthening and δ weakening cortical representations, but the mechanism underlying this distinction remains unknown.
In this study, we utilized a biophysical thalamocortical model capable of learning neural sequence memories during wakefulness and producing spontaneous memory replay during SWS to study the distinct roles of SO and δ activity. Specifically, we implemented a model that shifts between SO and δ activity during SWS by varying intrinsic calcium dynamics in pyramidal cells, and measured consolidation of a single sequence memory in a cortical region while it received interfering inputs from other brain regions, including traces of recent hippocampal memories. First, our model implementation suggested that SO and δ waves tend to exhibit Up states with distinct temporal durations, a prediction which we were able to confirm through analysis of in vivo rodent data. Second, we found that the longer Up states characteristic of SO activity permitted cortical activity to recover from perturbations and return to the memory attractor representing the original memory trace. This recovery promoted cortical memory replay, preserved, and even further consolidated the memory representation despite substantial interference. In contrast, the shorter Up states during δ activity were dominated by perturbing inputs, preventing attractor recovery and resulting in weakening of the cortical memory trace. Slow-wave properties, including Up state duration, are regulated by multiple brain systems, particularly neuromodulatory circuits. Our results predict that the brain employs active mechanisms, potentially mediated through astrocytic calcium signaling, to bias sleep reactivation toward either consolidation or forgetting, controlling the balance between memory exploitation and exploration depending on behavioral demands.

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Poster

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Title: Neural dynamics of visuo-prefrontal cortical interactions during visual rule formation

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Abstract: The medial prefrontal cortex (mPFC) is known to encode abstract rule representations through schematic, experience-dependent mechanisms. However, the neural mechanisms by which mPFC and sensory regions interact to form such representations through sensory-reward experience remain poorly understood. Moreover, rule representations formed during waking experience must be stabilized through sleep-dependent memory consolidation, a process involving hippocampal sharp-wave ripples (SWRs) and sleep spindles that coordinate hippocampal-neocortical interactions. Whether and how SWRs and spindles interact for cortical-cortical rule formation and consolidation remains unclear. Here, we conducted high-resolution *in vivo* electrophysiological recordings from mPFC, secondary visual cortex (V2), and hippocampal CA1 region in rats over five days of a light-reward association task, in which a flickering light predicts water reward. We characterize these processes at the level of cell assemblies by examining how coordinated activity across mPFC and visual cortex is organized during waking rule encoding, and how it is replayed for consolidation during subsequent sleep. Theta power in mPFC and V2 during the light-reward association task showed a progressive and coordinated increase across learning days, suggesting the emergence of a shared oscillatory framework for rule representation across visuo-prefrontal circuits. In contrast, HPC showed distinct dynamics from mPFC and V2, raising the question of whether hippocampal engagement is necessary for visuo-prefrontal rule representation. These findings motivate further investigation into the cell-assembly level mechanisms of visuo-prefrontal rule encoding and its consolidation through hippocampal-neocortical interactions during sleep.

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Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

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Topic: I.08. Learning and Memory

Support: UCI Drury Depression Institute LIFT-D 50k

Title: Closed-loop stimulation reveals developmental trajectory of memory-related hippocampal-cortical communication

Authors: *L. MA[1], D. KHODAGHOLY[2], J. GELINAS[3,4];
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Abstract: Functionally mature long-term memory processes rely on precise coordination between the hippocampus (HC) and the neocortex (CX), in the form of temporal oscillatory coupling between hippocampal sharp-wave ripples (SWRs) and cortical oscillations. However, neither the presence of these oscillations nor the capacity for long-term memory are innate to the

immature brain. We hypothesized that functional maturation requires early expression of communication patterns between emergent ripple-band oscillations in the developing HC-CX network. To this end, we first characterized the developmental trajectories of local field potentials (LFP) and neural spiking patterns recorded simultaneously from HC and CX in unanesthetized pups across the first postnatal weeks. Cortical fast ripple-band oscillatory activity (CXRs) emerged and developed in parallel with maturation of SWRs. CXRs and SWRs robustly recruited local neural firing and gradually expressed temporal coupling at ages earlier than the behavioral expression of functional spatial memory consolidation capacity assessed using an object location memory task. We then implemented and validated a closed-loop electrical stimulation protocol for modulating the developing HC-CX network. SWRs-triggered pulse stimulation delivered to the ventral hippocampal commissure truncated SWRs with high sensitivity and specificity in the immature hippocampus, altering cortical responsivity in a developmentally-regulated manner. These results have implications for our understanding of critical periods for maturation of memory networks and the role of neural activity patterns in shaping this process.

Disclosures: L. Ma: None. **D. Khodagholy:** None. **J. Gelinas:** None.

Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

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Topic: I.08. Learning and Memory

Support: FG27738

Title: Closed-loop optogenetic manipulation of the hippocampal-nucleus reuniens-prefrontal network across memory phases

Authors: *F. SVIRSCHEVSKI[1], S. SHAO[1], J. FERRERO LOPEZ[1], T. KAWANO[2], D. KHODAGHOLY[1], J. GELINAS[1];
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Abstract: Memory consolidation is reliant on coordinated activity in the hippocampus (HC) and medial prefrontal cortex (mPFC). The nucleus reuniens (RE) of thalamus, which anatomically exhibits direct reciprocal connectivity to both regions, is a candidate structure mediating this communication. To investigate its role, we performed in vivo electrophysiology in rats during non-rapid eye movement (NREM) sleep. We identified ripple-like oscillations in the RE (100-180 Hz; mean duration 45 ms) associated with robust thalamic spiking and phase-locked to both hippocampal sharp wave-ripples (SPW-R) and mPFC ripples. Importantly, coupling between HC and mPFC ripples was consistently accompanied by co-occurring RE ripples, and the strength of this tri-coupling scaled with memory demand, suggesting a modulatory role for the RE in oscillatory synchronization during memory consolidation. To causally test this hypothesis, we

employed closed-loop optogenetics to inhibit the RE at the time of SPW-R during consolidation or reconsolidation phases of a cheeseboard memory behavior task across recent (next-day test) and remote (7-day interval) memory paradigms. AAV-CamKII-NpHR-eYFP virus was injected into the RE, followed by implantation of electrodes in HC and RE and an optic fiber targeting RE. Real-time SPW-R detection triggered laser delivery to disrupt RE activity during consolidation. We observed decreased network synchrony between mPFC, RE, and HC after optogenetic inhibition of RE at SPW-R onset compared to sham virus-infected rats as well as compared to within-subject open-loop control sessions (identical but not SPW-R-locked stimulation) and no-stimulation sessions. By means of HC-RE-mPFC circuit manipulation in this experiment, we propose a role of the RE as a critical node in sleep-dependent memory consolidation.

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Poster

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McCance Fellowship

Title: Firing Rate Homeostasis Promotes Computation and Learning Through Irregular Spiking

Authors: *H. LI[1], D. LEVENSTEIN[2];
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Abstract: Neuronal spiking in the mammalian forebrain is highly irregular, at cell-specific low rates constrained by homeostatic plasticity. Whether this irregularity reflects noise or an underlying computational mechanism remains unclear. To examine the relationship between firing rate homeostasis, spiking statistics, and computational performance, we trained recurrent spiking neural networks with eligibility propagation (e-prop) to solve reinforcement learning tasks, including standard benchmarks and a naturalistic foraging task. We found that networks trained with spike rate homeostasis consistently outperformed those trained without it, with faster, more reliable learning and often better performance. Furthermore, we found optimal task performance when neurons maintained a target firing rate, rather than globally minimizing spiking activity. These target firing rate networks had more irregular spiking, with super-Poisson multi-modal ISI distributions resembling those seen in cortical neurons in vivo. Across multiple tasks, the best performing networks were found at the target firing rate that also produced the most irregular spiking, and networks' spike irregularity and task performance were significantly correlated. Compared to firing rate-minimizing networks and non-homeostatic networks,

networks with target firing rate homeostasis had a broad distribution of firing rates, with activity distributed among the population rather than restricted to a small number of neurons. These results suggest a close relationship between firing rate homeostasis, irregular spiking, and computation, in which firing rate homeostasis serves to maintain an optimal regime for learning whose signature is irregular spiking, rather than simply minimizing energy expenditure.

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Poster

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Topic: I.08. Learning and Memory

Title: Hippocampal-like representation of space emerges in a deep reinforcement learning agent trained in naturalistic, egocentric environments

Authors: *V. VANCHINATHAN, D. LEVENSTEIN;
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Abstract: The hippocampus represents where an animal is in its environment, with spatially tuned cells and a population-level manifold that maps environmental and task geometry. During planning and resting states, the hippocampus simulates plausible trajectories through the environment, called “replay”, which are thought to support learning. Previously, we found that recurrent neural networks trained to predict sensory observations as an agent moves through an environment develop both capacities, suggesting that predictive learning may be a good algorithmic description of hippocampal operations. However, it remains unknown how the hippocampus supports complex behavior in large environments with multiple interacting goals. Model-based reinforcement learning systems, such as the DreamerV3 algorithm, learn goal-directed behavior in complex environments and rely on an internal “world model” (WM), which is also a recurrent network that learns through predictive learning and is used to train a policy network offline. We thus wondered if these WMs develop a spatial representation of the environment like seen in the hippocampus. To test this, we trained DreamerV3 agents to play a modified version of Crafter, an open-world reinforcement learning benchmark in which an agent must collect resources to unlock hierarchical achievements while maintaining homeostatic needs like thirst, hunger and energy. We made Crafter more naturalistic by making the observation and action space egocentric. To make DreamerV3 a better model, we also added biologically-inspired constraints: non-negative activity with restricted synaptic and energy resources in the form of weight decay and activity regularization. We found that the agent’s position in a familiar environment was linearly-decodable from neural activity in the recurrent WM, and that many WM neurons were reliably active in specific locations in the environment. Of these, many neurons showed place-cell-like representations, with one or more place fields and a wide range of field widths. Intriguingly, we found that the world model of agents trained across multiple

environments represented the agent's position in novel, unseen environments. Spatially reliable neurons in this model also exhibited place-cell-like representations, despite no previous exposure to the testing environment. Together, these results suggest that the WM of model-based RL agents is analogous to the hippocampus, and that predictive learning in multiple different environments gives WMs the ability to map unseen environments with no additional learning.

Disclosures: V. Vanchinathan: None. **D. Levenstein:** None.

Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR379.15/LL13

Topic: I.08. Learning and Memory

Support: Computational Postdoctoral Fellowship, Wu Tsai Institute
R01EY035127
R21AG087186
P30EY026878

Title: Spatiotemporal Scaling of Sleep-like Cortical Off-States during Wake

Authors: *A. SCHNEIDER[1], J. A. CARDIN[2], D. LEVENSTEIN[3];
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Abstract: OFF-states, or transient periods of inactivity in populations of cortical neurons, are generally associated with sleep but have also been reported during wakefulness. Alternating OFF and ON states have been linked to learning and synaptic homeostasis, particularly during sleep. However, their spatial scale, laminar organization, and relationship to arousal are poorly understood during wake in rodents.To characterize wake OFF-states across cortex, we combined Neuropixels recordings with simultaneous mesoscopic calcium imaging. Acute recordings were obtained from 10 head-fixed C57BL/6 mice expressing R-CaMP. Neuropixels probes targeted primary visual cortex across cortical depth, while widefield calcium imaging monitored activity across the dorsal cortical surface. We developed an OFF-state detection framework integrating single-unit, high-gamma, and local field potential signals to identify and precisely localize population silencing events.Wake OFF-states were significantly modulated by behavioral state, occurring less frequently during locomotion or whisking than during quiescence. OFF-states exhibited coherent temporal organization across deep cortical layers, revealed by conditional probability and correlation analyses of independently detected events on individual recording sites. Simultaneous mesoscale imaging demonstrated that OFF-states propagate across cortex and span a continuous, heavy-tailed distribution of spatial and temporal scales. Longer-duration OFF-states were associated with broader cortical propagation. Despite these coordinated dynamics, wake OFF-states were generally shorter and less completely silent than those

observed during sleep, suggesting that elevated arousal constrains large-scale cortical silence during wakefulness.To examine how sleep pressure shapes these dynamics, we developed a complementary preparation combining chronic EEG monitoring, sleep deprivation, and head-fixed Neuropixels-mesoscopic recordings. Preliminary observations indicate that elevated sleep pressure promotes larger, longer-lasting, and more spatially distributed OFF-states accompanied by neural signatures of reduced arousal. These approaches provide a framework for defining how cortical OFF-states emerge across the transition from wakefulness to sleep.

Disclosures: A. Schneider: None. **J.A. Cardin:** None. **D. Levenstein:** None.

Poster

PSTR379: Developmental and Sleep-Dependent Reconfiguration of Learning Circuits

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR379.16/LL14

Topic: I.08. Learning and Memory

Title: Sleep-like pruning improves network performance and synaptic efficiency in artificial neural networks

Authors: *I. V. RAO[1], D. LEVENSTEIN[2];
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Abstract: During sleep, structural turnover occurs in cortical circuits, selectively eliminating and forming new synaptic connections in a process thought to support memory consolidation while preserving capacity for new learning. Whether and how such turnover shapes network performance and synaptic efficiency remains unresolved. To test this, we developed SleepPrune, a development- and sleep-inspired structural plasticity algorithm for artificial neural networks in which synapses are pruned and regrown after every training epoch. With SleepPrune, connection density decreases over the course of training and reaches steady state with constant synaptic turnover. We then investigated how this dynamic pruning supports learning in feedforward and recurrent networks trained on image classification tasks with gradient descent. Networks trained with SleepPrune were remarkably robust to pruning, maintaining equivalent performance to fully connected networks at less than 1% connectivity, and outperformed sparse initialization and state-of-the-art pruning algorithms. This robustness was enhanced by unreliable synapses and synaptic resource constraints, features often regarded as biological limitations. In addition to improving synaptic efficiency, dynamic pruning improved network performance. Networks with ~5-10% connectivity outperformed dense networks, indicating that sparsity confers benefits beyond optimizing synaptic resources. When regrowth was biased toward potential connections whose weight changes would most improve performance, this accuracy advantage extended to sparser regimes. To understand what changes beyond accuracy, we analyzed recurrent activity at different sparsities using population geometry, single-unit selectivity, and fixed-point analysis. Reducing connection density produced a systematic shift in network dynamics: intrinsic timescales lengthened and effective dimensionality declined, and recurrent activity transitioned

from high-dimensional trajectories to compact, convergent flows, suggesting slower, more stable computation. Dynamic structural plasticity therefore provides a mechanism for robust, efficient learning in sparse networks.

Disclosures: I.V. Rao: None. **D. Levenstein:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.01/LL15

Topic: I.09. Spatial Navigation

Support: NIH R01 MH120073

Title: Logarithmic speed scaling and novelty-related modulation of acetylcholine dynamics in hippocampal region CA1

Authors: *J. FANG, J. H. WILMOT, M. E. HASSELMO;
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Abstract: Acetylcholine (ACh) released from medial septal projections modulates hippocampal dynamics during active exploration. Although ACh has long been linked to memory encoding, recent work suggests that septo-hippocampal cholinergic signals also carry movement-related information. We tested whether extracellular ACh release in hippocampal region CA1 follows the compressive speed scaling observed upstream in the septal system, and whether this movement baseline can provide a framework for evaluating novelty-related modulation. We expressed GRAB-ACh3.0 in CA1 and recorded fluorescence with fiber photometry while mice freely explored open fields under alternating light-on and light-off conditions. Tracking and photometry were analyzed in 0.2-s bins using linear mixed-effects models. Across 48 sessions in 5 mice, CA1 ACh fluorescence increased robustly with locomotor speed. A model using ln(speed) fits the ACh-speed relationship better than a raw-speed model, indicating that the increase in ACh with speed follows a saturating exponential function (logarithmic scaling). Lightness versus darkness showed a small negative effect on mean fluorescence in darkness and had a very small moderation effect. These findings show that CA1 cholinergic dynamics follow a saturating exponential function with movement speed. and that ambient illumination can weakly modulate this mapping during free exploration. To ask whether CA1 ACh also reflects novelty-related exploration, we performed pilot analyses of responses to novel objects using frame-wise exploration criteria based on nose proximity to the object boundary, head orientation toward the object, and exclusion of climbing/crossing events. In a pilot study comparing novel to familiar objects, object-directed exploration and CA1 ACh fluorescence were numerically biased toward the new object. In a separate test across days, exploration-related ACh was also numerically higher during the first exposure (day 1) than a repeat exposure (day 2). These preliminary observations are consistent with the possibility that novelty-related events add residual

modulation beyond locomotion, but larger and more fully counterbalanced experiments are needed to separate object novelty, location novelty, and speed-related effects. Together, these results establish a quantitative movement-speed baseline for testing how hippocampal ACh multiplexes locomotor and novelty-related information during memory-guided exploration.

Disclosures: J. Fang: None. **J.H. Wilmot:** None. **M.E. Hasselmo:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.02/LL16

Topic: I.09. Spatial Navigation

Support: NIH Grant MH120073
NIH Grant MH139270

Title: Visual landmarks dissociate postrhinal and medial entorhinal spatial reference frames during place navigation

Authors: *P. A. LACHANCE[1], E. R. GROSS[3], S. SANKARANARAYANAN[2], M. E. HASSELMO[2];
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Abstract: Animals use first-person (egocentric) sensory information to update internal representations of their environments and guide navigation relative to remembered locations. Neuronal representations of space are often defined from a top-down, world-centered (allocentric) perspective, such as the preferred firing locations of hippocampal place cells or entorhinal grid cells. A major source of visuospatial input to the hippocampal formation is the postrhinal cortex (POR), which contains neurons sensitive to the egocentric bearing and/or distance of environmental boundaries (EB cells) and projects strongly to the medial entorhinal cortex (MEC) which contains grid cells and other neurons with allocentric spatial receptive fields. While spatial representations in these regions have been compared during random foraging, it is not known how POR and MEC differentially encode elements of the surrounding environment during navigation relative to a learned place. We initially used tetrodes to record neurons from POR and MEC as animals repeatedly navigated to a learned but visually imperceptible allocentric location in the environment (‘goal zone’), entry into which led to random scattering of sucrose pellets throughout the environment to encourage full sampling of the space. Neither POR EB cells nor MEC grid cells overrepresented the goal zone with their firing preferences. Further, shifting a prominent visual landmark while keeping the goal zone stationary caused POR cells to shift their directional preferences with the landmark, while MEC cells stayed anchored to the allocentric reference frame. We next used Neuropixels probes to record simultaneously from POR and MEC as animals completed a modified task where the goal

zone and visual scene always shifted together. The results were the same: POR representations tended to shift with the visual landmark, whereas MEC representations remained in register with the allocentric reference frame, rather than the goal zone. These results suggest: 1) that POR and MEC representations are not significantly biased toward a behavioral goal; 2) that POR neurons will ignore a behavioral goal to track a visual landmark; and, 3) that MEC cells will ignore a behavioral goal to track the animal's 'true' position within the overall room. Future experiments will be needed to determine how POR and MEC coordinate their egocentric versus allocentric reference frames and contribute cohesively to goal-directed navigation.

Disclosures: P.A. LaChance: None. **E.R. Gross:** None. **S. Sankaranarayanan:** None. **M.E. Hasselmo:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.03/LL17

Topic: I.09. Spatial Navigation

Support: CIHR Project Grant #8401226
CIHR Project Grant #367017
CIHR Project Grant #377074
CIHR Project Grant #463403

Title: Predictive coding and representational dynamics in the hippocampus during learning

Authors: M. YAGHOUBI[1], ***J. C. ROBINSON**[2], M. P. BRANDON[3];
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Abstract: The hippocampus forms predictive representations of future events, yet the population-level mechanisms underlying their emergence remain poorly understood. In a recent study, we demonstrated that at the single-cell level hippocampal reward representations progressively shift backward from reward locations to earlier task states during learning, giving rise to predictive coding of reward. Here, we investigate the broader reorganization of hippocampal population activity that underlies this phenomenon. Using calcium imaging of CA1 neurons across weeks of learning, we tracked the evolution of spatial and task-related representations at both single-cell and population levels. We found that hippocampal population codes undergo continuous backward reorganization across learning. This reorganization was not uniformly distributed across the task. Instead, the strongest changes occurred preceding behaviorally salient features, including choice-relevant cues and reward locations. At the single-cell level, place fields systematically shifted backward, while population-level analyses revealed coordinated displacement across the entire state space. This reorganization was not explained by random representational drift which is thought to be driven with the turnover of PCs. Aligning

place fields across trials or sessions abolished much of the apparent population displacement. Across learning, backward reorganization transformed hippocampal state space such that neural activity at a given location increasingly resembled representations of future task states. This generated predictive population codes that anticipated upcoming salient events and mirrored the temporal structure of learning. Next, we examine whether entorhinal cortex (EC) layer III output is required for the emergence and stability of these predictive representations. To address this question, we combine calcium imaging with optogenetic manipulation. Specifically, we express the opsin Chrimson in EC layer III neurons of pOxr1-Cre mice and test whether perturbation of EC layer III activity alters the temporal evolution of predictive hippocampal reward representations across learning. Together, these studies identify continuous backward reorganization as a fundamental principle governing hippocampal representational dynamics and help to define the circuits that support the emergence of predictive coding during learning. Rather than passively encoding current experience, hippocampal population codes are reshaped through learning to predict future task-relevant states, linking synaptic plasticity, representational change, and predictive computation.

Disclosures: M. Yaghoubi: None. **J.C. Robinson:** None. **M.P. Brandon:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.04/LL18

Topic: I.09. Spatial Navigation

Support: CIHR

Title: An intrinsic evolving hippocampal scaffold guides the encoding of novel spatial memories

Authors: *J. KARIMI ABADCHI[1], J. LEE[2], M. BRANDON[1];
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Abstract: Computational models propose that the hippocampus maintains an adaptive generative model of the world. The model is updated by the experience, which in turn guides the subsequent learning. A key prediction of this account is that the day-to-day evolution of offline and online neural activity should be coordinated as an animal learns. To test this, we used longitudinal miniscope calcium imaging and LFP recordings to track large neural populations in dorsal hippocampal CA1 of mice for weeks before and during the encoding of a novel environment. We found that offline hippocampal activity patterns evolve daily in a structured manner. Critically, the neural code during the first encounter with the novel environment was significantly more similar to the offline patterns from the immediately preceding homecage session than to those from days earlier. Moreover, the hippocampal offline activity seemed to seed and guide the formation of the spatial representation of a novel environment. This work aims to shed light on how the brain may use available internal activity patterns to facilitate learning.

Disclosures: J. Karimi Abadchi: None. **J. Lee:** None. **M. Brandon:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

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Program #/Poster #: PSTR380.05/LL19

Topic: I.09. Spatial Navigation

Support: NIH Grant R21AG087912
NIH Grant R00NS116129

Title: Hippocampal Acetylcholine Release Encodes Spatial Novelty and Correlates with Exploratory Behavior in CA1

Authors: *M. AZIZI[1], F. FAROKHI MOGHADAM[2], H. DANNENBERG[3];
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Abstract: Cholinergic signaling within the septo-hippocampal circuit is essential for memory, arousal, and locomotion-related processing of sensory information. Previous work demonstrated that the activity of cholinergic projection neurons in the medial septum/diagonal band of Broca is strongly correlated at behaviorally relevant timescales with an animal's movements and with exploring novel object locations (Kopsick et al., 2022; Moghadam et al., 2025). However, these studies did not directly measure hippocampal acetylcholine (ACh) release, leaving unanswered to what extent sub-second ACh release dynamics are correlated with animal movement, behavior, and spatial novelty encoding. Here, we used a genetically encoded ACh sensor (GRAB-ACh3.0) combined with fiber photometry to record ACh release dynamics in CA1 of 3–6 months old female mice alongside 3-D kinematic tracking of mouse behavior to identify and quantify correlations between sub-second ACh release dynamics during free-foraging, novel environment exposure, and an object location memory (OBLOM) task. Consistent with previous GCaMP studies, CA1 ACh release was strongly correlated with the logarithm of running speed (n = 4 mice, 50 sessions). Additionally, acetylcholine signaling exhibited sustained elevations during exploratory and attentively engaged behaviors, including rearing, and sustained suppression during grooming and eating, behaviors associated with lower exploratory demands. Furthermore, ACh release increased during exploration of objects in novel locations relative to familiar locations, suggesting that phasic ACh release contributes to the encoding of novel object-place associations (n = 4 mice, 16 sessions). Lastly, exploration of a novel arena induced a sustained increase in CA1 ACh release across the entire running speed range. Notably, the positive correlation between ACh release and movement speed was preserved under both conditions (n = 2 mice, 10 sessions), indicating that environmental novelty enhances cholinergic activity independent of locomotion speed. Together, these findings show that hippocampal ACh release is correlated with exploratory behavior and spatial novelty encoding.

Disclosures: M. Azizi: None. **F. Farokhi Moghadam:** None. **H. Dannenberg:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.06/LL20

Topic: I.09. Spatial Navigation

Title: Beyond Rate: Hippocampal Phase Codes for Space and Memory

Authors: *L. D. KOLIBIUS[1], M. S. HERMILLER[2], A. BRANDT[3], M. F. KHAZALI[4], M. J. KAHANA[5], H. BOWMAN[6], S. HANSLMAYR[7], J. JACOBS[1];
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Abstract: Place cells and concept neurons are canonical examples of rate coding: they are identified because neurons fire more often at certain locations or in response to particular people or objects. We asked whether a complementary phase code is present in spike timing within the theta cycle: when a neuron fires relative to the 3–12 Hz theta rhythm. Such a code could reveal task information in neurons that do not pass firing-rate tuning criteria.We analyzed three single-neuron datasets to test whether this is a general feature of hippocampal coding: human virtual navigation to test spatial coding and population readout, rodent linear-track navigation to test cross-species generalization, and human image viewing to test whether the principle extends beyond space to semantic memory content.
In human virtual navigation, theta firing phase carried spatial information. Eleven of 135 phase-testable hippocampal neurons showed position-related phase tuning (p=0.032). This effect survived when removing candidate rate-place neurons at a threshold of $p \leq 0.05$ and $p \leq 0.20$ (both $p < 0.05$). Thus, position information was visible in spike timing among neurons that would not be labeled as place cells by rate criteria. The strongest evidence for an independent phase contribution came from population decoding: adding theta phase to firing rate improved spatial decoding accuracy (p=0.004), and the improvement persisted when phase information from candidate rate-place neurons was excluded. Theta phase therefore added spatial information not already captured by the rate-place population.
We next asked whether this signal generalized across species. In rodent hippocampal linear-track recordings, the same analysis recovered robust phase-place tuning across pooled and direction-specific traversals, including after rate-place neurons were excluded. This shows that phase-based spatial information is not specific to human virtual navigation. Finally, we asked whether phase coding extends beyond navigation. In human image viewing, neurons fired at specific theta phases after image onset, including neurons not identified as canonical rate-defined concept neurons. This extends the effect from spatial to visual-semantic.

Together, these results support a broader view of hippocampal coding: firing-rate labels identify the most visible coding neurons, but theta firing phase reveals additional task information across species and modalities, including in neurons often treated as noncoding under rate-only analyses.

Disclosures: L.D. Kolibius: None. **M.S. Hermiller:** None. **A. Brandt:** None. **M.F. Khazali:** None. **M.J. Kahana:** None. **H. Bowman:** None. **S. Hanslmayr:** None. **J. Jacobs:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

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Program #/Poster #: PSTR380.07/LL21

Topic: I.09. Spatial Navigation

Support: Advanced ERC grant project ID 101142587
SFB Transregio 384
DAAD Scholarship

Title: Improved tuning, impaired function: Alcohol induces a hyper-persistent theta rhythm and sharpens spatio-temporal coding in the septo-hippocampal-entorhinal network

Authors: *D. CHOWDHURY, D. A. A. MACLAREN, M. I. SCHLESIGER, B. THROM, N. BIEBER, H. MONYER;
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Abstract: Alcohol intoxication impairs episodic and spatial memory, processes mediated by the septo-hippocampal-entorhinal network. After confirming that 1.7 g/kg alcohol impairs spatial memory, we used in vivo electrophysiology in the medial entorhinal cortex (MEC), dorsal hippocampus, and medial septum (MS) to investigate the underlying neural mechanisms. While all regions are affected, we found that MEC is particularly susceptible with pronounced reductions in firing rates across excitatory and inhibitory neurons, and in the network-level excitation-inhibition balance. Spatially selective cells demonstrate a preferential suppression of out-of-field spikes, resulting in a paradoxical improvement in tuning precision. Similarly, the speed coding fidelity increases across regions. This enhanced tuning with reduced variability is accompanied by increased theta phase locking, reflecting synchronized, metronome-like firing. At the network level, a hyper-persistent theta rhythm with reduced frequency and increased cycle count drives this rigidity. These findings suggest that alcohol impairs memory by causing a shift towards a rigid, hyper-persistent state. [D.C. and D.A.A.M. contributed equally]

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Poster

PSTR380: Hippocampal Dynamics and Coding

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.08/LL22

Topic: I.09. Spatial Navigation

Support: Lundbeck Foundation

Title: A conserved medial septal population sequence defines a theta-scaled temporal code across brain states and days

Authors: *M. DOU[1], M. VILA-MARTÍN[2], P. C. PETERSEN[3];
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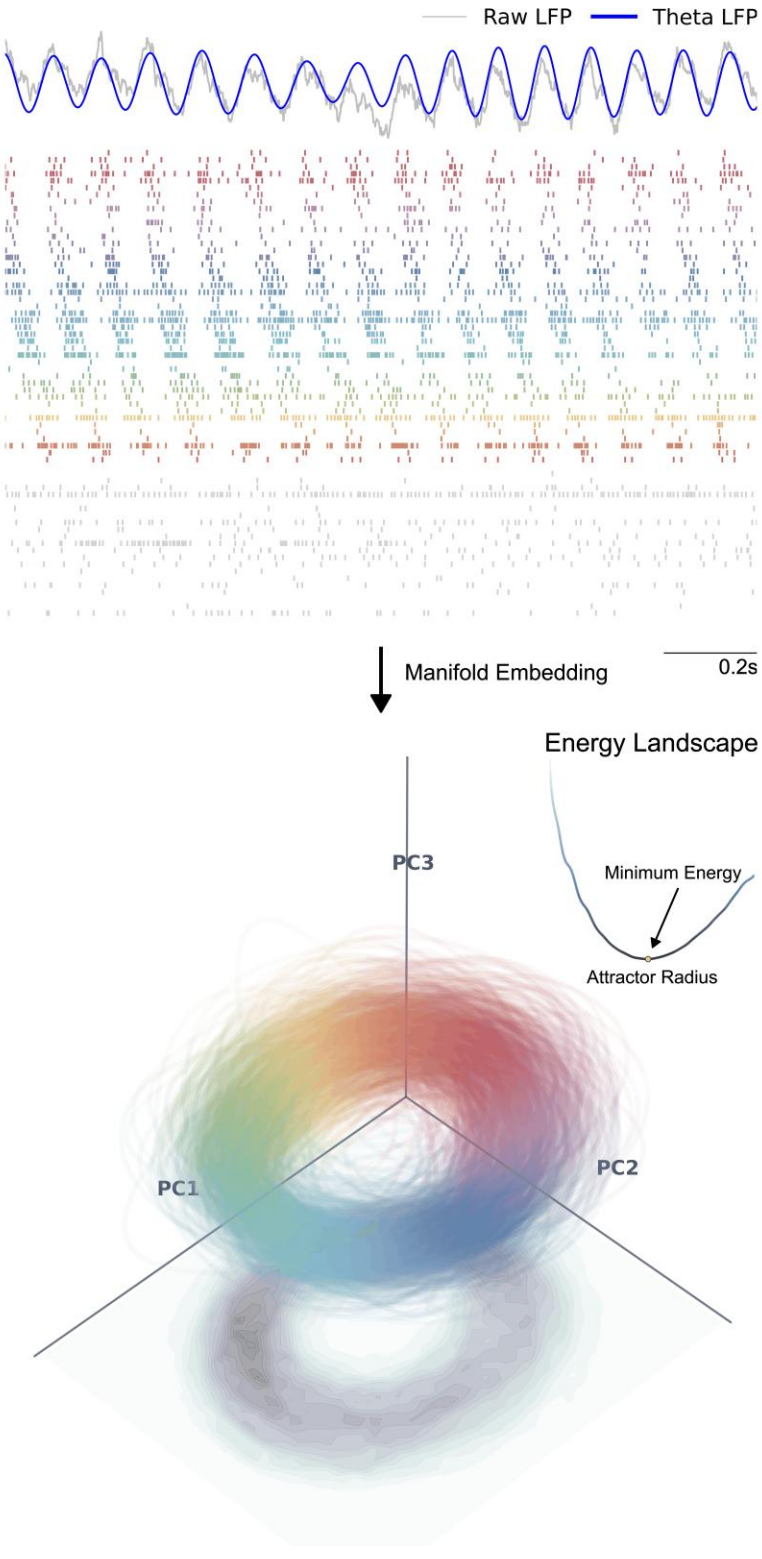
Abstract: The hippocampal theta oscillation depends critically on the medial septum, but how septal population activity organizes theta timing remains unclear. Rather than acting as a synchronous pacemaker, the medial septum may coordinate hippocampal timing through structured population dynamics. Using chronic dual Neuropixels recordings from medial septum and hippocampus in freely moving rats, we find that septal theta timing is organized by a conserved population sequence.

During active locomotion, medial septal activity forms a ring-like low-dimensional state space. The leading population components oscillate at theta frequency with a quarter-cycle offset, defining an intrinsic circular phase coordinate. This coordinate reveals a reproducible, internally referenced sequence conserved across individual theta cycles and trials.

The sequence is conserved across states and days. During REM sleep, medial septal activity forms a similar ring that aligns with the RUN manifold after a rigid rotation. During NREM sleep, discrete events re-express the same sequence and preserve the RUN population plane, while remaining separable from sharp-wave ripple windows. Across days, matched neurons retain sequence order and theta-plane geometry.

Together, these observations indicate that medial septal theta is organized as a conserved limit-cycle-like dynamic: across waking behavior, REM sleep, NREM events, and days, septal activity progresses through a stable circular state space whose phase defines a reproducible sequence. This population phase also carries hippocampal timing information beyond LFP phase. Medial septal population phase predicts hippocampal place-cell spiking beyond behavior, spike history, and hippocampal LFP phase, indicating that the septal sequence captures timing structure not fully explained by the local hippocampal oscillation.

These findings suggest that the medial septum provides an internally referenced population clock for hippocampal theta timing, organized by conserved sequential dynamics rather than homogeneous synchronous pacemaking.



Disclosures: M. Dou: None. **M. Vila-Martín:** None. **P.C. Petersen:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

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Program #/Poster #: PSTR380.09/LL23

Topic: I.09. Spatial Navigation

Support: NRDI ADVANCED 153546
National Academi of Scientist Education
Hungarian Research Network

Title: Differential coupling of medial septal neurons to hippocampal layers.

Authors: K. NEMETH, M. JELITAI, G. TARCSAY, K. PETRIK, ***V. VARGA**;
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Abstract: Theta oscillation is indispensable for integrating inputs in the hippocampus during encoding and retrieval. Medial septal (MS) GABAergic neurons broadcast a multiphasic oscillatory signal impinges upon inhibitory neurons in the hippocampal formation. Timing of inhibition gates inputs to pyramidal cell compartments, coordinates hippocampal output with its targets and enables the multiplexing of different operational modes. Functional subgroups of inhibitory neurons can be defined by theta phase preference both in the hippocampus and in the MS. This observation led us to hypothesize that the multiphasic theta-rhythmic output of the MS may correspond to parallel, time-delayed inhibitory streams essential for orchestrating activity in pyramidal cell compartments. Here, we tested this hypothesis by simultaneously recording the MS and hippocampus utilizing high-density silicone probes (Neuropixels 2.0) in awake, head-fixed mice. We characterized association of MS neuronal activity with hippocampal theta sampled from all layers of dorsal CA1 by phase coupling strength (mean vector length), ordinary correlation, wavelet-based coherence and transfer entropy. We have uncovered differential coupling of MS theta rhythmic neurons to theta from different hippocampal layers. The coupling profile calculated for every MS neuron defined layer-preferring subgroups. We have also observed divergent time-delays between MS neuronal activity and theta from layers independent from layer-defined coupling. Optogenetic suppression of parvalbumin-expressing GABAergic MS neurons, the core theta pacemakers, resulted in uneven reduction of theta power without altering the phase-profile across layers. Our results support the assumption that the septo-hippocampal connection is composed of parallel, time-delayed oscillatory streams differentially controlling inhibition of pyramidal cell compartments.

Disclosures: K. Nemeth: None. **M. Jelitai:** None. **G. Tarcsay:** None. **K. Petrik:** None. **V. Varga:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.10/LL24

Topic: I.09. Spatial Navigation

Support: NIH Grant R01AG076198
Biotechnology and Biological Sciences Research Council. Grant BB/T014768/1

Title: Boundary Vector Cells Encode a Future-Biased Spectrum of Positions in the Rat

Authors: *E. L. NEWMAN[1], Z. TIGANJ[2], C. LEVER[3];
[1]Indiana Univ. Bloomington, Bloomington, IN; [2]Indiana Univ., Bloomington, IN; [3]Univ. of Leeds, Leeds, United Kingdom

Abstract: Spatial tuning is a hallmark property of neural firing in the hippocampal formation. Yet, that tuning is often less well correlated with the instantaneous current position of an animal than it is with an integrated version of the past or future state of the animal. Whether that encoding is biased toward past or future states and the extent to which it shows fixed versus multi-scale encoding varies across circuits and cell types. The temporal encoding properties of boundary vector cells of the subiculum are not well established. To address this here, we re-analyzed recordings of boundary vector cells (BVCs) described previously by Lever et al. (2009) with multiple approaches. In the first, we asked if adding a temporal offset between the rat position and the spiking of a BVC increased the apparent spatial tuning in the firing rate map. We found that aligning BVC spiking with future states maximized the rate map spatial tuning. These results were mirrored in a second analysis that, instead of optimizing rate map spatial tuning, optimized how well the firing rate map predicted the BVC spiking. The second analysis also allowed us to ask whether that encoding is focused on a particular temporal horizon or whether the encoding captures behavior at multiple scales. To this end, for a given recording, we asked “How much time-integration of the behavioral state is the observed spiking most consistent with?” We observed a wide spectrum of time-constants of integration across cells, indicating that BVCs form a multiscale encoding of future states. The distribution of both offsets and integration rates observed across BVCs did not differ significantly from other, non-BVC, subiculum neurons. Taken together, these findings indicate that BVCs, along with other subiculum neurons, form a multi-scale encoding of future states.

Disclosures: E.L. Newman: None. **Z. Tiganj:** None. **C. Lever:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.11/LL25

Topic: I.09. Spatial Navigation

Support: NIH R21MH135251
NSF 2534735

Title: Hippocampal contributions to spatial memory during rearing, locomotion, and reward epochs

Authors: *M. LI[1], R. TROHA[3], E. L. NEWMAN[2];
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Abstract: Prior work has emphasized the importance of locomotion and reward epochs in the study of how hippocampal activity relates to spatial memory. This is based on findings of strong correlations between hippocampal activity and behavioral state during these epochs. However, recent data from our lab show that inactivating the hippocampus during rearing epochs impairs spatial memory, demonstrating that such attentive-sampling from place behaviors are key moments of hippocampal dependent spatial memory encoding. The importance of these attentive-sampling epochs relative to locomotion or reward epochs is unknown. In part, this is because causal experiments testing the necessity of hippocampal activity during these epochs remain lacking. This is a significant gap in our understanding. To address this gap, here we performed an experiment designed to directly compare the consequences of inhibiting hippocampal processing during rearing, locomotion, or reward collection for spatial memory. Using a real-time closed-loop optogenetic silencing approach, we induced behavior-triggered inactivation during detected bouts of rearing, locomotion, or reward collection during the study phase of a delayed-win-shift radial arm maze task and measured the effect on memory performance in the test phase. This project tests, for the first time, whether hippocampal activity during epochs long assumed to be central to hippocampal-dependent memory encoding is indeed necessary. The results presented here inform artificial models of memory and active sensing, and guide translational and computational approaches to memory dysfunction.

Disclosures: M. Li: None. **R. Troha:** None. **E.L. Newman:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.12/LL26

Topic: I.09. Spatial Navigation

Support: NIH R21MH135251
NSF 2534735

Title: Hippocampal CA1 Ensemble Dynamics During Rearing in Spatial Exploration

Authors: *R. TROHA[1], S. SULLIVAN[2], K. BOND[2], V. M. GARZA[2], E. L. NEWMAN[2]; [1]Dept. of Psych. and Brain Sci., Indiana Univ. Bloomington, Bloomington, IN; [2]Psychological and Brain Sci., Indiana Univ., Bloomington, IN

Abstract: Spatial navigation is integral to normal, healthy living in humans and animals. Spatial navigation relies heavily on a normally functioning hippocampus. A key feature of spatial navigation is the ability to encode sensory information from the surrounding environment. However, little is known regarding when the hippocampus encodes sensory information during navigation to create or update the cognitive map.

Studies show a relationship between the hippocampus and rearing on the hind legs, an exploratory behavior during which animals are thought to encode sensory information. For example, hippocampal theta power is elevated during rearing. In addition, a sink in the dentate gyrus and enhanced theta-fast-gamma coupling were observed during rearing (Barth et al., 2018). More recently, our lab showed that optogenetic inhibition of the hippocampus during rearing impairs performance in a spatial working memory task (Layfield et al., 2023). These results suggest that hippocampal function during rearing has an important role in spatial memory. However, it remains unclear how neural ensembles in the hippocampus function during rearing to form or update the cognitive map.

To address this gap, we examined single-unit hippocampal CA1 activity during rearing in an open field exploration experiment. Animals were tested across six days. On days 1-3, animals completed three sessions each day, all in the same environment (context A). On days 3-6, animals completed six sessions each day, where the context followed an order of A-A-B-B-A-C. That is, in the first two sessions, animals were placed in the familiar context A. In sessions 3 and 4, animals explored the same arena, but with a copper mesh floor (context B). In session 5, animals explored context A again. Lastly, in session 6, four white walls were added around the perimeter of the field, providing a distal cue change (context C). Here, results address the following questions: 1) Is there a unique neural state during rearing? 2) Does rearing improve the accuracy of where a rat thinks it is? These results improve our understanding of how and when the hippocampus processes spatial information during navigation.

Disclosures: R. Troha: None. **S. Sullivan:** None. **K. Bond:** None. **V.M. Garza:** None. **E.L. Newman:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.13/LL27

Topic: I.09. Spatial Navigation

Support: Hutton Honor's College Research Grant

Title: Rearing and Head Scanning as Functionally Equivalent Information-Seeking Behaviors

Authors: *D. BURKS[1], R. TROHA[3], E. L. NEWMAN[2];
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Abstract: Spatial memory is crucial for navigation and adapting to changing environmental conditions. Known neurophysiological mechanisms of spatial memory center on the importance of hippocampal activity and its spatial tuning. Yet, the behavioral strategies that support adaptive spatial encoding remain poorly understood. We have shown that dorsal hippocampal activity during rearing is necessary for spatial working memory, highlighting a role of information seeking behaviors for spatial memory encoding. Similarly, spatial tuning by dorsal hippocampal neurons is substantially updated during another information seeking behavior: attentive head scanning. However, the functional relationship between these behaviors is unknown. Here, to assess the relevance of environmental context for the expression of these behaviors, we quantified rearing and head scanning in a radial-arm-maze spatial working memory task while manipulating the height of the maze walls. Our goal was to test whether the stereotyped patterns of rearing that rats generate with tall walls are replaced with attentive head scanning when the walls are short enough to reach the top without rearing. We found that rats reared significantly less often when the walls were shortened and, instead, exhibited frequent attentive head scanning. The head scanning was done when and where the rats had previously exhibited stereotyped rearing. These results support the hypothesis that rearing and head scanning are functionally related behaviors. Future work should test two key inferences: 1) Head scanning is a critical epoch of spatial memory encoding, and 2) Spatial tuning by hippocampal neurons is updated during rearing.

Disclosures: D. Burks: None. **R. Troha:** None. **E.L. Newman:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.14/LL28

Topic: I.09. Spatial Navigation

Support: NIH Grant 1F31AG087649-01
AFAR/McKnight Award

Title: Prior experience accelerates reward over-representation in novel environments to support learning-to-learn.

Authors: *A. M. BAGGETTA[1], A. PIERRELOUIS[2], N. YAMAGUCHI[2], E. VAN DER RIJN[2], B. M. SWEIS[2], B. KO[2], D. MEDEIROS[2], D. J. CAI[2];
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[2]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Across a lifetime, animals encounter countless environments and experiences that shape future learning. The hippocampus is thought to encode these experiences through distinct internal neuronal representations, or cognitive maps, to form memories of different environments. How the hippocampus accumulates and integrates multiple cognitive maps to support learning-to-learn is poorly understood. To ask how the dorsal CA1 (dCA1) region of the hippocampus supports learning-to-learn, we developed a spatial navigation paradigm where mice (n = 15, 9 females, 6 males) ran along a circular track to forage for water rewards. Within each track, there were two ports that delivered water and another six ports that were not rewarded. Mice formed long-lasting memories of the reward port locations and recall of these reward locations was hippocampus dependent. To follow how dCA1 activity evolves as mice accumulate cognitive maps across environments, we used our open-source head-mounted Miniscope to image dCA1 calcium activity while mice learned reward locations on four distinct circular tracks, spending five days on each before advancing to the next. To control for experience with a circular track, a control group spent 15 days on a single track before its final track. Mice exhibited learning-to-learn, acquiring reward locations more rapidly on successive tracks. After learning stabilized on the first track, a higher proportion of place fields concentrated around rewarded locations (reward over-representation), as expected. Prior experience with multiple tracks enhanced this effect: on subsequent tracks, a greater proportion of cells showed peak activity near reward locations, these reward-associated representations stabilized faster, and cells near reward locations carried more spatial information. Together, these data suggest that experience across multiple environments accelerates the allocation of highly spatially informative cells to important locations in novel environments, a circuit-level correlate of learning-to-learn.

Disclosures: A.M. Baggetta: None. **A. PierreLouis:** None. **N. Yamaguchi:** None. **E. van der Rijn:** None. **B.M. Sweis:** None. **B. Ko:** None. **D.J. Cai:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.15/LL29

Topic: I.09. Spatial Navigation

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National Institute of Neurological Disorders and Stroke, R01NS13585002

Title: Complementary encoding of spatial location and environmental structure in hippocampal CA1 and subiculum

Authors: *E. XU[1], J. M. OLSON[1], A. JOHNSON[2], L. CHANG[3], E. TAO[1], D. A. NITZ[1];
[1]UCSD, San Diego, CA; [2]Univ. of Michigan, Ann Arbor, MI; [3]Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: The hippocampal formation supports spatial navigation through neural representations of location, orientation, and trajectory. While hippocampal area CA1 is well known for precise place coding, the role of dorsal subiculum (SUB) remains less understood. To compare spatial representations in these regions, we recorded neuronal populations from CA1 and SUB while rats performed a spatial working-memory task on a complex "Triple-T" maze containing overlapping routes and repeated structural motifs. CA1 neurons primarily encoded specific locations and trajectory-dependent information. In contrast, SUB neurons frequently generalized across spatially separated but structurally analogous maze locations. Individual SUB neurons often exhibited firing fields at locations sharing similar directional or topological properties, whereas CA1 neurons rarely showed such recurrence. Population analyses revealed stronger correlations between analogous route segments in SUB than in CA1 and reduced trajectory dependence during overlapping route traversal. Both regions reliably encoded location, but SUB represented space at a larger scale than CA1. In addition, transitions in SUB ensemble representations aligned closely with maze intersections and path-segment boundaries, suggesting segmentation of environmental structure into functional "chunks." In contrast, CA1 transitions were distributed throughout path segments and were more trajectory specific. These findings demonstrate complementary coding schemes in CA1 and SUB. CA1 preferentially differentiates unique trajectories and locations, whereas SUB emphasizes generalized structural relationships across environments. The results support a role for subiculum in encoding higher-order environmental organization that complements hippocampal place coding during navigation.

Disclosures: E. Xu: None. **J.M. Olson:** None. **A. Johnson:** None. **L. Chang:** None. **E. Tao:** None. **D.A. Nitz:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.16/LL30

Topic: I.09. Spatial Navigation

Support: R21

Title: Adaptation of Anterior Thalamic and CA1 Neurons Following Maze-Environment Reorientation

Authors: *M. DING[1], R. J. PLACE[2], D. A. NITZ[3];
[1]UC San Diego, La Jolla, CA; [2]Cognitive Sci., UCSD, La Jolla, CA; [3]Univ. of California San Diego, San Diego, CA

Abstract: Animals constantly navigate their environment to find food, remember potentially dangerous places and return to their point of departure. In many environments, travel is constrained or organized along specific pathways whose intersections and orientations to each other can be learned. In such contexts, knowledge of the organization of available environmental pathways is key to success in defining the appropriate trajectory to initiate toward a target location from any given starting location. To model this, we constructed a hexagonal shaped maze with intersecting pathways forming a grid of triangles and three major axes of travel. We employed a task demanding small versus large triangle-shaped trajectories whose selection depended on the location of twelve different, trial-specific start sites. With multiple manipulations of maze-environment spatial and orientational relationships, we show that the alignment of maze axes to the axes of the experimental room boundaries is critical to task performance. Importantly, the impairments observed in animal performance following 30-degree orientation shifts over early manipulation sessions were later replaced by near-baseline accuracy as the animal adapted over training. Our next question has been to determine what allows navigational adaptation to the realignment of maze relative to the environment. To address this, we recorded anterior thalamic nucleus (ATN) and CA1 neurons during 30-degree shifts and examined the adaptation of their spatial and directional tunings relative to pre-shift (baseline) sessions. Many ATN neurons exhibited directional tuning relative to experimental room boundaries and preferred tuning orientations appeared to be stable across baseline and maze rotation sessions. CA1 neurons exhibited primarily place-specific activity that encoded analogous positions along triangle-shaped routes that partially overlapped and that shared the same directional series. Following maze rotation, approximately half of all CA1 neurons exhibited place-specific activity selective to the baseline or 30-degree rotation sessions, consistent with global remapping. However, the remainder exhibited organized remapping, maintaining firing locations relative to the room or maze or in exhibiting 90-degree rotations consistent with the 90-degree change in alignment of maze and experimental room axes.

Disclosures: M. Ding: None. **R.J. Place:** None. **D.A. Nitz:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

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Program #/Poster #: PSTR380.17/LL31

Topic: I.09. Spatial Navigation

Support: NIH R01 NS135850-02
NIH R21 MH135321-01A1

Title: Directionally-tuned neurons in subiculum dynamically engage with the theta rhythm

Authors: *R. J. PLACE[1], D. A. NITZ[2];
[1]UCSD, La Jolla, CA; [2]Univ. of California San Diego, San Diego, CA

Abstract: Activity within the Subiculum (SUB) has typically been defined as an extension of CA1, with SUB firing patterns appearing as theta-rhythmic multiplexed “place fields”. Unlike CA1, SUB spatial tuning is often stable across changing environments and, recently, SUB neurons have been found to track topographic structures, including environmental axes and corners. It is yet unknown how these unique SUB responses are integrated into the CA1 temporal theta framework.We recorded simultaneous SUB and CA1 activity in rats as they traversed a series of interconnected paths. A novel task required rats to learn routes defined amongst a network of three path axes that intersect to form a triangular grid, with the starting location dictating the given trial’s rewarded route. We found maze-room orientation served to guide behavior, and the path arrangement allowed us to test orientational and positional effects on neural activity. SUB firing patterns displayed multiple forms of directional tuning during task navigation, with single vs multi-peaked tuning defined by the maze structure. SUB neurons displayed strong intra-network coordination, which was driven by the variety directionally tuned neurons. SUB coordination, and directional tuning, was largely lost during post-task open-field recordings.SUB directional activity dynamically responded to the theta rhythm, with in-field activity displaying a range of responses defined by strong theta modulation and phase-precession, versus those appearing largely unrhythmic. SUB theta relationships varied across tuning fields, with multi-fielded cells’ theta-engagement depending upon the directional field to which it was defined. While spikes within some directional fields displayed phase-locking , activity within other fields was found to phase-precess relative to route location, which suggest aspects of multi-directional activity is encoded into HPC’s temporal framework. We found that the variety of SUB rate and phase responses improved decoding for unique route combinations. SUB’s directional activity, in fact, formed a contextually relevant spatial code that is distinct from CA1 and is optimized to guide learned behavior in complex environments.

Disclosures: R.J. Place: None. **D.A. Nitz:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.18/LL32

Topic: I.09. Spatial Navigation

Title: Theta phase dynamics of task-specific firing in the subiculum during navigation on a 12-arm radial maze

Authors: *J. NGUYEN[1], E. GALANG[1], D. A. NITZ[2];
[1]Cognitive Sci., UC San Diego, San Diego, CA; [2]Cognitive Sci., Univ. of California San Diego, San Diego, CA

Abstract: Across hippocampal and cortical systems encoding spatial and action variables in the environment, the hippocampal theta frequency oscillation has been identified as a temporal framework by which to integrate spatial tuning in different forms. Within the hippocampus, CA1

place cells exhibit theta phase precession (TPP), a mechanism that sequentially orders inputs from cells and facilitates spike-timing-dependent plasticity. When TPP is disrupted, animals exhibit severe spatial learning deficits even when place-specific firing remains intact. As the primary output of CA1, the subiculum receives these temporally ordered spatial sequences, yet its own encoding is qualitatively different. Rather than strictly representing specific places or directions, subiculum neurons exhibit schematic task-phase firing, which was found when examining the animal's integration of the environment across stable trajectories in different orientations on the 12-arm radial maze. The maze and task together allowed assessment of tuning to location, orientation, and position along the route independently. Animals were adept at navigating inverted U-shaped trajectories across shifting task modes, successfully adjusting to varied angular displacement between visited arms (e.g., 30°, 60°, 90°, 120°, or 150° offsets). Because subiculum neurons fire for task variables rather than strictly for direction or place, this serves as an opportunity to examine spike-phase relationships outside of traditional spatial mapping. Initial analyses across subiculum neurons point to variation between the use of phase locking and phase precession to differentiate task-relevant variables. This approach may reveal how non-spatial task-phase specific tuning is integrated into the overall spatial framework, using TPP to order non-spatial responses into trajectories necessary for episodic memory.

Disclosures: J. Nguyen: None. **E. Galang:** None. **D.A. Nitz:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.19/LL33

Topic: I.09. Spatial Navigation

Title: Adaptation of Spatial and Multi-Directional Tuning of Dorsal Subiculum Neurons to Rotation of Task-Defined Versus Environment-Defined Spaces

Authors: *S. KIM[1], R. J. PLACE[2], Q. DING[3], D. A. NITZ[4];
[2]Cognitive Sci., [1]UCSD, La Jolla, CA; [3]UC San Diego, La Jolla, CA; [4]Univ. of California San Diego, San Diego, CA

Abstract: To further investigate the characteristics of spatial, directional and multi-directional tuning of subiclulum (SUB) neurons and their role in spatial cognition, we recorded single unit activity in SUB and CA1 simultaneously while animals traversed 6 pathways within a triangle-grid patterned path network with boundaries in the shape of a hexagon. The 6 pathways were organized into identically shaped pairs that demanded all left-turning versus all right-turning actions. The navigational task linked 5 starting positions at the perimeter to goal positions also at the perimeter. Travel from the former to the latter demanded movement through the path network's center. In this way, task performance yielded unique directional transitions with the full set of routes covering all possible transitions in increments of 60 degrees. The path network and task designs allowed us to examine the rules governing multi-directional tuning in SUB and

recurrence in spatial tuning of SUB neurons over geometrically identical paths requiring different actions, directions of travel, and sequences of environmental locations. Further, we examined SUB and CA1 activity in rats following rotations of the full task structure, as achieved by rotating the start and goal positions by 60-, 120-, or 180-degrees mid-session. This allowed us to test the extent that directional versus spatial aspects of SUB versus CA1 cognitive maps would re-organize to changes in task orientational demands and to determine whether directional tuning in SUB would take reference to the environment, to the space defined by the task structure, or both. We observed robust tuning of individual SUB neurons to multiple directions of movement during task performance and encoding of path network locations affording transitions between different movement direction combinations. SUB neurons also exhibited complex forms of spatial tuning organized by maze and task structure that differed from the location-mapping observed in CA1 populations.

Disclosures: S. Kim: None. **R.J. Place:** None. **Q. Ding:** None. **D.A. Nitz:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.20/LL34

Topic: I.09. Spatial Navigation

Title: Subiculum in the latent space: from unimodal head-direction and place inputs to relational spatial and directional tuning

Authors: *K. M. SHANNON[1], D. A. NITZ[2];
[1]Cognitive Sci., UCSD, San Diego, CA; [2]Univ. of California San Diego, San Diego, CA

Abstract: The subiculum is considered a primary output of the hippocampal formation and a point of connectivity between thalamo-cortical and hippocampal/entorhinal systems for mapping locations, orientations, and trajectories. Recent findings indicate that subiculum encodes relationships between recurring sets of orientations and analogous environmental locations. This takes the form, for example, of axis tuning wherein subiculum neurons are active for headings in one direction and that direction's opposite (180^{o} preferred orientation offset). Subiculum neurons also exhibit recurrence in firing at path network locations that share similarity in geometric composition and position within a trajectory. Primary subiculum inputs include the CA1 sub-region of hippocampus known for trajectory-dependent location-specific tuning and the anteroventral thalamus, whose neurons often exhibit robust unimodal tuning to head orientation. How the subiculum composes these simple inputs into multi-location, multi-directional codes is unresolved. Can these codes emerge from a latent-variable model within its latent space? To examine this, we developed a recurrent latent-variable model whose latent state is interpreted as the subiculum, integrating its inputs along the animal's recorded trajectories. Inputs comprise anterior-thalamic head direction, CA1 place fields, and an angular velocity signal. The model is fit to predict subiculum population activity recorded during complex multi-path spatial working-

memory tasks. We assess whether the two signature phenomena (i.) directional-relationship tuning and (ii.) spatial-analogy tuning emerge in the latent units without being explicitly coded. The open-arena condition provides a built-in falsification test (the model must reproduce the loss of axis tuning), while input ablations identify the inputs/environmental regularities each code requires. In complex multipath environments, subiculum neurons, unlike their CA1 inputs, (i.) recur at analogous but spatially separate locations defined by path structure, (ii.) span a range of spatial scales, (iii.) sustain firing across segment transitions, and (iv.) encode the axis of travel with bimodal tuning anchored to boundaries and released in an open arena. These established features define the model targets. Our findings suggest subiculum may operate at the level of schema encoding, converting fixed, low-level inputs into task- and geometry-dependent relational codes. Latent-variable models offer a candidate account of how subiculum composes such schemas, and broadly how spatial and directional relational structure can emerge from neural components.

Disclosures: K.M. Shannon: None. **D.A. Nitz:** None.

Poster

PSTR380: Hippocampal Dynamics and Coding

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR380.21/LL35

Topic: I.09. Spatial Navigation

Support: NSF GRFP

Title: Subicular encoding of schematic task phase and invariant structural motifs during navigation on the 12-arm radial maze

Authors: *E. GALANG[1], J. NGUYEN[1], D. A. NITZ[2];
[1]UC San Diego, San Diego, CA; [2]Univ. of California San Diego, San Diego, CA

Abstract: Navigation requires the ability to generalize the structure of the environment across spatial contexts. To support this generalization, the hippocampal formation must provide a framework to bridge the gap between its location encoding and action-execution in the cortex. The subiculum sits at a critical junction, receiving major input from both CA1 and anterior thalamus (ATN). Prior work has established a qualitative dissociation between these regions, where the subiculum exhibits weaker place-specific tuning and uniquely represents geometric corners, environmental borders, and axes of travel despite its proximity as the immediate output of CA1.
The present study uses a 12-arm radial maze task and recordings in the subiculum and its circuitry along the thalamo-cortical axis to examine the integration of the environment across stable trajectories in different orientations. The maze and task together allowed assessment of tuning to location, orientation, and position along the route independently. Animals were adept at navigating inverted U-shaped trajectories across shifting task modes, successfully adjusting to

varied angular displacement between visited arms (e.g., 30°, 60°, 90°, 120°, or 150° offsets). Results reveal further support of the dissociation between these regions; while CA1 outputs stereotypical place signals, the subiculum encodes task phase: generalized inflection points representing recurring structural motifs that remain invariant regardless of the animal's global position. These results challenge the view of subiculum as a simple relay of CA1 distributing a compressed version of its place map, instead serving as a site of multi-sensory integration that maps invariant features including task phase and axes of travel. Together, results suggest that the subiculum assembles these features into a structural scaffold, providing a schema by which motor cortices navigate complex, multi-axial environments.

Disclosures: E. Galang: None. **J. Nguyen:** None. **D.A. Nitz:** None.

Poster

PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.01/LL36

Topic: I.08. Learning and Memory

Support: NIH Grant R01MH122391
NIH Grant U19NS107616
FY2025 Finding a Cure for Epilepsy and Seizures

Title: Extrinsic control of hippocampal ripples by entorhinal and thalamic inputs to CA1

Authors: *N. PALEOLOGOS, M. VOROSLAKOS, R. P. MACHOLD, A. LOBELLO, B. RUDY, G. BUZSAKI;
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Abstract: Hippocampal ripples have been extensively studied for their role in memory consolidation and retrieval. The canonical sharp wave-ripple is generated by intrinsic hippocampal inputs: CA3 pyramidal cell population bursts induce excitatory currents arriving at the mid-apical dendrites in the stratum radiatum (RAD; “sharp wave”), accompanied by local interactions between CA1 pyramidal cells and interneurons that drive high-frequency oscillations (“ripples”). Our lab (Paleologos et al., 2025) and others (Castelli et al., 2025) have recently described another version of ripples characterized by excitatory currents in the stratum lacunosum-moleculare (LM) prior to the ripple peak in the pyramidal layer. These events exhibit lower ripple peak frequencies and power and delayed recruitment of CA3 cells compared to traditional sharp wave-ripple events. Given that glutamatergic projections from both the entorhinal cortex and thalamic nucleus reuniens terminate onto the distal apical dendrites of pyramidal cells, the primary source of excitation during LM ripples remains unknown. Furthermore, many of these projections target specialized interneurons in LM, particularly neurogliaform cells whose volume transmission of GABA and highly collateralized projections

across the hippocampal transverse axis can mediate widespread inhibition of extrahippocampal afferents. To assess the role of these circuits in gating extrahippocampal input and LM ripple genesis, we have simultaneously recorded from the dorsal hippocampus (1024-channel, 8-shank SiNAPS probes), nucleus reuniens (4-shank Neuropixels), and medial entorhinal cortex (4-shank Neuropixels) in head-fixed mice. These experiments enabled us to determine the relative contribution of excitatory entorhinal and thalamic spiking activity toward the generation of LM ripples with extensive spatial coverage of the dorsal hippocampus, thereby allowing accurate separation of LM and RAD ripples based on their distinct current-source density profiles. We also use transgenic mice (NDNF-flox-Flpo; VGAT-Cre; Ai80) to selectively target NDNF-expressing interneurons in the LM, corresponding to putative neurogliaform cells, via closed-loop optogenetic stimulation. In these experiments, light delivery is triggered by the detection of a current sink in LM that precedes supra-threshold increases in ripple power (100-250 Hz) in the CA1 pyramidal layer. Our findings will elucidate the network mechanisms distinguishing LM ripples from RAD ripples and the role of neurogliaform cells in gating excitatory, extrahippocampal inputs to the distal apical dendrites of CA1 pyramidal cells during resting states.

Disclosures: N. Paleologos: None. **M. Voroslakos:** None. **R.P. Machold:** None. **A. LoBello:** None. **B. Rudy:** None. **G. Buzsaki:** None.

Poster

PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.02/LL37

Topic: I.08. Learning and Memory

Title: Anatomical propagation organizes the temporal structure of hippocampal replay

Authors: *S. RAFILSON[1], M. VOROSLAKOS[2], N. PALEOLOGOS[3], J. GONZALEZ[4], A. H. WILLIAMS[1], G. BUZSAKI[5];
[1]New York Univ., New York, NY; [2]NYU, New York, NY; [3]NYU Grossman Sch. of Med., Brooklyn, NY; [4]Dept. of Psychiatry, New York Univ. Grossman Sch. of Medicine, New York, NY, USA, New York, NY; [5]Neurosci., New York University, Langone Med. Ctr., New York, NY

Abstract: Learning and memory support flexible animal behavior by enabling animals to use past experiences to predict the consequences of future actions (O'Keefe & Nadel, 1978). During consummatory behaviors and NREM sleep, theta sequences are replayed during sharp wave-ripples (SPW-Rs) and are thought to reflect a memory consolidation process (Wilson & McNaughton, 1994). While hippocampal replay has traditionally been studied as a point-source process, SPW-Rs can be global population-level burst events (Nitzan et al., 2022) and propagate along the septotemporal axis of the hippocampus (Patel et al., 2013; Payne et al., 2021). Because

of the spatiotemporal nature of SPW-Rs, we asked if hippocampal replay was similarly organized across anatomical space. We hypothesized that the temporal direction of replay (forward vs reverse) corresponds to the anatomical direction of propagation across the septotemporal axis of the hippocampus. To test this hypothesis, we recorded from two 4-shank Neuropixels probes parallel to the longitudinal axis, while rats slept and ran on mazes. Spatial decoding analysis revealed that hippocampal replay consisted of spikes from cells distributed across anatomical space and that the temporal direction of replay corresponded to the direction of anatomical propagation in SPW-Rs. Latent state sequence modeling revealed the existence of other, non-maze-related sequences that are replayed during ripples and whose temporal direction corresponds with anatomical propagation. We propose that the extent of the longitudinal axis provides a substrate for sequence generation in the hippocampus, and that sharp wave ripples replay sequences in time by spreading activity across anatomical space.

Disclosures: S. Rafilson: None. **M. Voroslakos:** None. **N. Paleologos:** None. **J. Gonzalez:** None. **A.H. Williams:** None. **G. Buzsaki:** None.

Poster

PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.03/LL38

Topic: I.08. Learning and Memory

Support: Marie Skłodowska-Curie grant agreement No 892957, EU
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Title: Functional Coupling of Midline Thalamic Neurons to the Prelimbic Cortex and the Ventral Subiculum

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Abstract: The midline thalamus (MT) consists of a group of “non-sensory” nuclei implicated in arousal regulation during motivated behavior and the sleep-wake cycle. The MT provides an interface for subcortical afferents and for higher-level cortical and hippocampal afferents, originating primarily from the prefrontal cortex (PFC) and the ventral subiculum (VS). Yet very

little is known about how specific MT nuclei interact with cortical and hippocampal activity across the sleep-wake states. We performed large-scale unit recordings from MT neurons in Calretinin (CR)-Cre mice during unrestrained sleep-wake behavior, while simultaneously recording population activity from the PFC and VS. Combining post-hoc histology with ChR-2-assisted optical identification of CR neurons and their projections to VS and PFC, we segmented the MT into four anatomically distinct regions. MT unit activity exhibited a strong correlation with sleep-wake states and substates. During NREM sleep, the MT neurons exhibited a marked infraslow activity, oscillating between high-firing tonic and low-firing bursting modes; tonic firing across neurons signaled behavioral microarousals. This infraslow fluctuation was ubiquitous across the MT and anticorrelated with the vSub population activity. Neurons in the paraventricular nucleus (PVT) has lower firing rates and were less bursty than neurons in other nuclei. These differences could be explained by electrophysiological differences between CR-expressing and non-CR neurons, as well as by their relative fractions in different MT nuclei. Furthermore, distinct MT nuclei were differentially coupled to cortical DOWN states (DS). The majority of MT units were suppressed during DS. Suppression of activity was the longest in the PVT and the earliest in the nucleus reuniens (RE), preceding cortical DOWN states. With the exception of PVT, MT nuclei exhibited strong rebound synchronous bursts of spikes with the strongest rebound activity observed in the RE, possibly triggering cortical DSs.Hippocampal sharp-wave ripple-related activity showed a strong increase in the anterior part of the MT, particularly in the PVT, while units in the posterior MT and in the RE were overall suppressed. Finally, we found a substantial number of theta-modulated units across the MT during both REM and active WAKE, with the highest modulation magnitude in the anterior paratenial nucleus (PT) and surrounding PVT regions. Our findings demonstrate that distinct MT nuclei exhibit marked differences in intrinsic and circuit properties and are selectively coupled to neocortical and subicular activity.

Disclosures: G.S. Komlósi: None. **J. Gonzalez:** None. **M. Voroslakos:** None. **P. Vizi:** None. **L. Biro:** None. **L. Jae hyun:** None. **J. Cheon:** None. **L. Acsady:** None. **G. Buzsaki:** None.

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Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.04/LL39

Topic: I.08. Learning and Memory

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NS142069

Title: Delineating the role of hippocampal excitatory-inhibitory interactions in learning

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Abstract: In navigation and memory tasks, the hippocampus's principal output, CA1, compresses complex sensory and mnemonic information into low-dimensional representations embedded in high-dimensional neuronal activity. While dimensionality-reduction methods can visualize these manifolds, the circuit mechanisms by which CA1 achieves remain unknown. We approached this question using a digital twin brain modeling approach. We recorded large-scale CA3 and CA1 recordings of mouse hippocampus with Neuropixels 2.0 probes before, during, and after novel maze learning, quantifying pyramidal-pyramidal (Pyr-Pyr) and pyramidal-interneuron (Pyr-Int) interactions. Next, we trained excitatory-inhibitory (E/I) recurrent neural networks (RNNs) to predict an animal's maze position from experimentally recorded CA3 population activity. This digital twin allowed us to explore how a biologically constrained CA1-like network could perform dimensionality reduction and context-dependent-learning. We found that trained RNNs produced emergent Pyr place tunings and unit wirings dominated by strong Pyr-Int motifs and sparse Pyr-Pyr connectivity, matching the known CA1 properties. In the experimental data, a linear readout of pyramidal cell activity weighted by Pyr-Int (but not Pyr-Pyr) synaptic transmission recovered low-dimensional signals encoding animal's position, speed, and trial number, suggesting that interneurons drive the hippocampal dynamics underlying CA1's low-dimensional task representations. Our pre/post-sleep learning and maze-remapping analyses revealed that Pyr-Pyr connections were more plastic, while Pyr-Int connections remained stable across sessions and environments. Digital twins reproduced this division of labor: Pyr-Pyr weights exhibited higher variability across trained networks than Pyr-Int weights across independent models or between learning two contiguous maze environments. Furthermore, neural perturbation of connectivity in digital twins provided new experimentally testable hypotheses. Together, our combined experimental and computational investigations indicate that CA1 balances stability and flexibility through complementary excitatory-inhibitory motifs, offering an efficient and biologically grounded algorithm for representations and learning.

Disclosures: J. Gonzalez: None. **M. Voroslakos:** None. **Z.S. Chen:** None. **G. Buzsaki:** None.

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PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.05/LL40

Topic: I.08. Learning and Memory

Support: 2U19NS107616-06

Title: Involvement of FOS-tagged neurons in communication subspaces in the dentate gyrus-medial entorhinal cortex

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Abstract: The dentate gyrus (DG) and medial entorhinal cortex (MEC) constitute a key cortico-hippocampal interface for spatial memory encoding, with MEC grid and related spatially tuned cells providing map-like spatial input that DG granule cells transform into sparse, more orthogonalized population codes via pattern separation. While individual neurons in both regions have been characterized extensively, how specific cells are recruited into low-dimensional population geometries, or communication subspaces, through which DG and MEC interact during learning remains poorly understood. Here we combine TRAP2-based molecular tagging with chronic dual-region electrophysiology to identify and track behaviorally activated ensembles across spatial learning in the DG-MEC circuit. Using TRAP2×Ai32 mice implanted with high-density silicon probes in DG and MEC, we record population activity as animals learn a place-reward association task. Optogenetic identification of FOS-tagged neurons allows for direct comparison of firing properties, theta and gamma entrainment, and alignment with DG-MEC population subspaces between tagged and untagged cells. Histology reveals consistent GFP labeling of cells in both regions, and preliminary recordings demonstrate our ability to opto-tag cells. We have found that opto-tagged cells exhibit higher firing rates than non-tagged cells, motivating our hypothesis that FOS-tagged neurons represent a distinct subset that may preferentially occupy stable subspaces that persist across learning. Importantly, histological analysis shows that FOS-tagged neurons are not randomly distributed but reside mainly in the superficial sublayer of the granule cell layer, forming an anatomically definable subspace. We predict that optogenetic reactivation of these ensembles will strengthen DG-MEC subspace coherence. By linking molecular identity to population geometry, this work aims to clarify how sparse, stable memory representations emerge from the dynamic DG-MEC circuit and to better understand early circuit-level mechanisms that may underlie spatial memory dysfunction.

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Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.06/LL41

Topic: I.08. Learning and Memory

Title: From labels to latents: revealing state-dependent computations and non-spatial replay with Jump Latent Variable Model

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Abstract: Neural activity is often interpreted by imposing external labels (e.g., position during locomotion) and decoding within that space (e.g. replay). While powerful, such supervision can mask structure in the data that do not correspond to the label. Unsupervised methods, in turn, often assume smooth latent dynamics and miss genuine discontinuities. We introduce a conceptually simple, computationally efficient latent variable model that infers both (i) the latent variables organizing population activity and (ii) whether their dynamics are continuous or fragmented in time. Fitting reduces to an expectation-maximization (EM) procedure that alternates two operations familiar to systems neuroscience—tuning-curve estimation and label decoding—without requiring external labels. Applied to rodent hippocampal recordings, our method identifies a continuity-fragmentation axis that characterizes population activity across sleep-wake brain states, modulated by cholinergic inputs. For a spatial navigation task, the model reveals distinct population patterns at the same physical position that supervised spatial decoding fails to detect. Moreover, the model enables replay analysis beyond spatial trajectories, and finds prevalent pre-play events associated with immobile and off-maze behaviors and post-task replay of locomotion. By not relying on externally imposed spatial labels, our approach exposes structure that supervised approaches obscure and provides a powerful tool for datasets lacking behavioral tracking.

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PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.07/LL42

Topic: I.08. Learning and Memory

Support: Simons foundation fellows to faculty award

Title: Medial prefrontal cortex constrains hippocampal forward theta sweeps to support impulse control during an auditory-spatial task

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Abstract: The medial prefrontal cortex (mPFC) exerts top-down control over goal-directed behavior and is functionally coupled to the hippocampus. Although both regions are implicated in flexible, decision-guided action, the circuit and network mechanisms by which this is implemented remain unclear. Past work has suggested that mPFC is necessary for cognitive control and may impact hippocampal theta sequences and hippocampal goal-related firing. However, how the mPFC regulates hippocampal activity on both coarse and fine timescales, and whether that maps onto goal-directed behavior, is an open question. Freely moving mice were trained to find water rewards on a linear track using an auditory cue that changes in frequency in a closed loop with their spatial position. Successful trials required mice to sustain attention to the tone and withhold licking until the target frequency was reached. Mice generally reached ~70% performance, with most errors occurring when mice undershot and licked before the target part. Analysis of these naturally occurring errors revealed a graded inverse relationship between the average decoded position on the track and the degree to which mice undershot. More impulsive trials showed a larger forward shift in decoded position relative to the animal's actual location. This observation raised the possibility that excessive hippocampal look-ahead reflects unconstrained sequence propagation in the absence of top-down control, rather than enhanced planning. To test whether mPFC contributes to this control, we transiently silenced mPFC while recording CA1 activity.mPFC was silenced by optogenetic activation of local PV+ interneurons while CA1 single-unit activity was recorded using high-density silicon probes as mice performed the task. mPFC silencing led to a marked decrease in performance, as it significantly increased premature or impulsive responses and decreased running speed. We observed a selective reduction in firing rates of CA1 PV+ interneurons, but only mild changes in place and goal-related firing fields. Analysis of position decoding recapitulated the baseline error-trial results: mPFC silencing led to position decoding that consistently shifted in front of the animal compared to control. Thus, mPFC silencing reproduced both the behavioral phenotype and hippocampal decoding signature of impulsive behavior. These findings suggest that mPFC constrains hippocampal look-ahead by regulation of local inhibition. In the absence of this top-down control, hippocampal representations become biased toward future locations, potentially uncoupling from ongoing behavior and promoting impulsive responding.

Disclosures: A. Ferreira Gomes Da Silva: None. **I. Zutshi:** None.

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PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.08/LL43

Topic: I.08. Learning and Memory

Support: NIH Grant 1F30MH143505-01

Title: The role of dopamine in hippocampal memory consolidation

Authors: *B. Y. LI[1], G. BUZSAKI[2];
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Abstract: The hippocampus is critical for the formation of long-term memories. According to the two-stage model of systems consolidation, awake experiences are encoded into the sequential activity of place cell assemblies and subsequently replayed during sharp wave ripples (SWRs). These SWRs serve as critical communication events between the hippocampus and the neocortex that enable the reorganization of experience into a high-dimensional cognitive map which supports adaptive and flexible behavior. During SWRs, neuronal activity replays sequences that occurred during behavior. This repetitive reactivation helps maintain the cognitive map and facilitates the generalization of knowledge across experiences by sharing replay spike content with the neocortex. While the majority of SWRs occur during non-rapid eye movement (NREM) sleep, previous work in our lab has demonstrated that awake SWRs can serve as a "tag" for subsequent consolidation by sleep SWRs. However, it remains unknown how specific sequences are selected for awake replay out of the many generated during behavior. Several lines of evidence point to dopamine as playing a crucial role in tagging behaviorally relevant experiences for subsequent consolidation. First, hippocampal place cells preferentially overrepresent reward locations in both spatial and non-spatial domains, and SWRs are enriched with replay of previously rewarded trajectories. Second, the stability of CA1 place fields has been shown to require D1/D5 dopamine receptor signaling, and direct infusion of dopamine agonists into the hippocampus improves spatial memory performance on recall tests. Third, the ventral tegmental area exhibits coordinated neural activity with awake, but not sleep, SWRs. Together, these findings support a role for dopamine in selectively tagging experiences for memory consolidation. We hypothesize that this tagging mechanism comes from dopamine's excitatory influence on hippocampal pyramidal cells, leading to the immediate reactivation of the spatial trajectories that precede reward, strengthening those assembly connections for subsequent repetition during NREM SWRs. To test this hypothesis, we train DAT::Cre mice to run on a modified radial eight-arm maze protocol and subsequently record fiber photometry signal using GRAB-DA in the dorsal hippocampus, striatum, and medial prefrontal cortex paired with electrophysiology using high-density silicon probes in the contralateral dorsal hippocampus.

Disclosures: B.Y. Li: None. **G. Buzsaki:** None.

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Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.09/LL44

Topic: I.08. Learning and Memory

Support: Simons Junior Fellowship

Title: Sharp wave-ripple clusters enhance hippocampal-neocortical engagement for memory consolidation

Authors: *C. LAFFERTY[1], M. VOROSLAKOS[2], G. BUZSAKI[3];
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Abstract: Hippocampal sharp wave-ripples (SPW-Rs), neocortical slow oscillations, and thalamocortical sleep spindles are hypothesized to provide a temporal framework for coordinated information transfer during memory consolidation. Hippocampal replay supports this process, yet replayed sequences often unfold across multiple SPW-Rs, suggesting that individual ripples may not constitute the fundamental unit of hippocampal output. Here, using large-scale electrophysiological recordings from the hippocampus and retrosplenial cortex, we show that hippocampal output is organized into clusters of SPW-Rs (cSPW-Rs) during UP states, which are often phase-locked to spindle troughs. Extending this approach with wide-field imaging and unsupervised latent-variable modeling, we found that cSPW-Rs enhanced segregation between the default mode and somatomotor networks and preferentially replayed spatially extended maze trajectories following learning. We propose that SPW-R clusters enable reverberating hippocampal-cortical spike exchange and the concatenation of sequential experiences, establishing ripple clusters as a previously unrecognized syntactic unit of hippocampal-neocortical dialogue.

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Location: WCC Halls A-C

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Topic: I.08. Learning and Memory

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Title: Hippocampal mechanisms supporting interactive vocal communication in Alston's singing mouse (S. teguina)

Authors: *Y. FUJISHIMA[1], J. DEL ROSARIO[1], Y. ZHANG[1], C. KEMERE[2], G. BUZSAKI[1], M. A. LONG[1];
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Abstract: The Alston's singing mouse (*Scotinomys teguina*) is a highly vocal rodent species that produces 6-10 s structured songs as part of territorial displays. Pairs of distant singing mice engage in coordinated vocal exchanges, suggesting a role in communication between neighboring home ranges in their native cloud forests. Although previous studies have shown that the orofacial motor cortex is required for a successful, temporally precise vocal response, how this acoustic social interaction is integrated into the cognitive map of territory remains unknown. Given that spatial and social information are computed within the hippocampal system, we performed chronic silicon probe recordings from the CA1-dentate axis of the dorsal hippocampus in the singing mouse. To our surprise, we found that as a mouse began to sing, sharp wave-ripples (SPW-Rs) occurred at a higher rate than previously observed in any behavioral state. Distinct dynamics of acetylcholine and oxytocin levels in the dorsal hippocampus, measured with GRAB sensors, further supported these brain state switches. Motivated by these observations, we examined population activity within dorsal CA1 and found that many neurons were preferentially active at a single location in the environment, indicative of traditional 'place cells'. We found that vocal encounters with conspecifics robustly induced the formation of new place fields oriented toward the location of a vocal partner in a subset of neurons. At the population level, place cells were strongly activated during singing-induced SPW-Rs, often representing spatially cohesive paths toward the direction of vocal partners. This work provides insight into the function of SPW-Rs during highly engaging social behavior and reveals a novel neural strategy by which the cognitive map rapidly tracks changes in a dynamic social environment.

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PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.11/LL46

Topic: I.08. Learning and Memory

Title: A neural manifold framework for understanding Fos expression during learning

Authors: *H. LO[1], J. BENVILLE[2], K. HANIN[2], R. BATISTA-BRITO[3], L. L. SJULSON[4]; [1]Dept. of Neurosci., Albert Einstein Col. of Med., New York, NY; [2]Neurosci. Dept., [3]Dept. of Neurosci., [4]Neurosci. Department, Psychiatry Dept., Albert Einstein Col. of Med., Bronx, NY

Abstract: Immediate early genes such as *c-fos* are widely used to label neuronal ensembles associated with learning. Fos expression is often interpreted as a marker of elevated activity, but firing rate alone does not fully explain which neurons become Fos-positive. We hypothesize that Fos expression reflects neural activity relative to intrinsic population dynamics, and that Fos-positive neurons mark a subset of the population representation that undergoes learning-related

plasticity. To test this, we combine longitudinal two-photon imaging, Fos reporters, and manifold analysis in the mouse medial prefrontal cortex (mPFC) during learning. Intrinsic manifolds are estimated from spontaneous activity during non-REM sleep to define on-manifold, non-manifold, and off-manifold subspaces. Preliminary analyses identify these subspaces in both mPFC electrophysiology and calcium imaging data. We are using dual-color imaging through a microprism to monitor calcium activity and Fos dynamics in the same neurons. We have validated that the GFP signal increases in the Fos-GFP mouse line after cocaine injection, and that we can record neuronal activity from the same population. We also developed a red-shifted, destabilized nuclear Fos reporter to enable longitudinal Fos tracking alongside green calcium indicators. To measure the learning-related Fos ensembles and neuronal dynamics, we have established a head-fixed Go/NoGo reversal task in combination with two-photon imaging, allowing us to record neuronal activity in the mPFC during learning and relearning. We will compare models in which subsequent Fos induction is predicted by absolute activity, activity relative to a static baseline, reward timing, or activity relative to the intrinsic manifold. We will also ask whether Fos-positive neurons contribute disproportionately to changes in task-variable representations across learning and reversal. This project links immediate early gene expression with the geometry of neural population activity, providing a framework for understanding how Fos contributes to experience-dependent circuit reorganization.

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PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.12/LL47

Topic: I.08. Learning and Memory

Title: Meditation modulates visual cortical plasticity and is linked to beta-band activity in resting EEG

Authors: *S. DAVANGER[1], M. WILHELMSEN BUGGE[1], T. RYGVOLD[2], H. EIFRING[1], T. ELVSÅSHAGEN[1], S. ANDERSSON[1];
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Abstract: Synaptic plasticity forms the basis for learning and memory and is impaired in several brain disorders. While permanently increased plasticity might be associated with instability and vulnerability, the prospect of plasticity-inducing short-term interventions has both scientific and clinical interest. Non-pharmacological, self-administered methods for stimulating synaptic plasticity in the human brain are few. To our knowledge, this is the first study to investigate how meditation is associated with short-term cortical synaptic plasticity. We investigated whether one

30 min session of nondirective meditation may increase visual evoked potential (VEP) plasticity in highly experienced practitioners, and whether such effects are associated with changes in EEG spectral activity. In a within-subject design, 32 highly skilled meditation participants underwent two 30-min sessions separated by one week: a meditation session and a control rest session. VEP plasticity was assessed using a visual stimulation paradigm, with responses measured at multiple post-stimulation timepoints. Resting-state EEG was analyzed to quantify frequency-specific power changes across frontal, central, and posterior regions. Meditation produced a modest amplitude enhancement of early VEP potentials following 2 min high frequency visual stimulation, increasing potentiation by approximately 14 % relative to control ($\Delta = 0.60$ μV, Cohen's $d = 0.32$, one-tailed $p = 0.049$). This effect was time-specific, diminishing at later timepoints. Inspection of individual responses revealed substantial inter-individual variability in the effect of meditation on plasticity, with indications of both responder and non-responder subtypes. Frequency-resolved EEG analyses did not reveal robust, group-level spectral differences between conditions. However, individual differences in central beta-band (13-30 Hz) power changes were positively associated with VEP plasticity. A median-split analysis further supported greater plasticity in participants with higher beta increases. These findings suggest that a self-administered, non-pharmacological intervention may facilitate short-term cortical plasticity, with considerable inter-individual variability linked to beta-band neural activity. Rather than reflecting a uniform effect, meditation appears to modulate plasticity in a temporally specific and physiologically differentiated manner. Our observations are compatible with the possibility that repeated meditation sessions facilitate recurring episodes of adaptive plastic reorganization of existing neural representations over time.

Disclosures: S. Davanger: Other; Volunteering as instructor in Acem meditation. **M. Wilhelmsen Bugge:** None. **T. Rygvold:** None. **H. Eifring:** Other; volunteering as instructor of Acem meditation. **T. Elvsåshagen:** None. **S. Andersson:** None.

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Location: WCC Halls A-C

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RIKEN CBS (T.J.M).

Title: Asymmetric Engram Network Reinstatement Underlies Unidirectional Memory Linking

Authors: *Y. SHI[1], T. J. MCHUGH[2];
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Abstract: Temporally proximal experiences are linked, allowing retrieval of one memory to influence recall of another. Previous studies suggest that memory linking is often unidirectional, such that recall of an earlier memory promotes retrieval of a later experience, but not vice versa. Although overlapping engram allocation has been proposed as a cellular mechanism for memory linking, how overlapping engrams contribute to unidirectional recall remains unclear. Here, we examined CA1 engram and non-engram population dynamics during encoding and retrieval of two temporally proximal object-context memories in mice to determine how engram activity shapes memory organization. Behaviorally, memory linking was observed only during retrieval of the earlier memory (context A), whereas retrieval of the later memory (context B) remained memory-specific. In an unlinked control group, where contexts A and B were separated by 24 h, mice formed distinct object-context memories. This asymmetry was independent of context order. Consistent with these findings, population activity during exploration of object B in context A was more similar to object B encoding activity than the reciprocal comparison in context B, indicating reinstatement of memory B during retrieval of memory A but not vice versa. Assembly analyses further supported asymmetric object-memory reinstatement. During encoding, context A engram cells were recruited during learning of context B, indicating engram overlap. Linked animals also exhibited greater similarity between context A and context B population activity patterns than unlinked controls. However, despite increased recruitment, these neurons showed reduced coactivity and lower network clustering. During retrieval in context B, context A engram networks exhibited weaker functional coupling and longer geodesic distances, indicating limited integration into the context B memory network. Together, these findings reveal that temporally proximal memories are linked in a unidirectional manner. Although overlapping engram allocation promotes representational similarity between memories, overlap alone is insufficient to ensure reciprocal recall. Instead, successful memory reinstatement depends on the network organization of overlapping engram populations, suggesting that memory linking is constrained not only by shared cellular allocation but also by the reinstation of memory-specific network architectures.

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RIKEN CBS (T.J.M)

Title: Deep entorhinal sublayer mediated feedback circuit dynamically modulates entorhinal-hippocampal network stability and episodic memory formation

Authors: *Y. LIU, V. SEKULIC, T. J. MCHUGH;
RIKEN Ctr. for Brain Sci., Wako-shi, Japan

Abstract: Objective and Rationale: Episodic memory relies on interconnected networks between the medial entorhinal cortex (MEC) and hippocampus (HPC). While previous studies focused on feedforward circuits from superficial MEC (sMEC) to HPC, the deep layer EC5b receives hippocampal output and projects back to sMEC, forming a continuous anatomical feedback loop. The functional logic of this EC5b-mediated circuit remains underexplored, particularly regarding how it maintains network stability and regulates memory strength. Here, we hypothesized that EC5b dynamically gates this cognitive loop. **Methods and Results:** We validated the Trib2-CreERT2 mouse line for specific EC5b targeting (specificity: 84.3%, efficiency: 91.7%; N=5). Rabies retrograde tracing revealed EC5b receives strong HPC inputs alongside broad cortico-thalamic modulation. To evaluate behavioral function, we applied chemogenetic manipulation (hM4D.Gi vs. mCherry controls with 0.1 mg/kg DCZ) in male mice undergoing weak Trace Fear Conditioning (wTFC), utilizing blinded, automated freezing scoring. EC5b inhibition significantly enhanced temporal memory ($p<0.05$, two-sided Mann-Whitney; N=14/group), whereas excitation impaired it. *In vivo* calcium imaging (EC5b: 620 cells, N=5 mice; EC3: 1808 cells, N=6; CA1: 5550 cells, N=13) revealed extreme EC5b firing sparseness, indicating a modulatory role. Strikingly, EC5b regulates the network state-dependently. During resting states, EC5b inhibition impaired spontaneous network stability, and during novel context exploration (low drive), it decreased EC3 and CA1 firing rates. However, during the aversive unconditioned stimulus (US, strong drive), EC5b inhibition caused significantly stronger EC3 activation. In CA1, cells co-responsive to the conditioned (CS) and unconditioned (US) stimuli showed enhanced activity, accelerating memory association within the first two trials by dis-constraining the network. **Conclusions:** These findings establish EC5b as a crucial, state-dependent feedback gate maintaining EC-HPC network stability. Under strong aversive drive, EC5b constrains hippocampal reactivation via feedforward inhibition; releasing this brake accelerates early learning. This biological mechanism provides a novel feedback-centered framework for spatiotemporal computational models. Furthermore, given the MEC's early vulnerability in Alzheimer's and altered inhibitory gating in schizophrenia, this deep circuit offers a vital mechanistic target for early neurodegenerative and psychiatric biomarkers.

Disclosures: Y. Liu: None. **V. Sekulic:** None. **T.J. McHugh:** None.

Poster

PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.15/LL50

Topic: I.08. Learning and Memory

Support: JSPS KAKENHI Grant-in-Aid for Early-Career Scientists (JP24K18613)

Title: CA3-CA1 Melanocortin Signaling Contributes to Hippocampal Memory

Authors: *E. TOMINAGA[1], Y. ZHOU[2], T. J. MCHUGH[3];
[1]Life Sci. and Med. Biosci., Waseda University, Grad. Sch. of Advanced Sci. and Engin., Tokyo, Japan; [2]RIKEN Ctr. for Brain Sci., Tokyo, Japan; [3]RIKEN Ctr. for Brain Sci., Wako-shi, Japan

Abstract: Glutamatergic transmission along the CA3-CA1 pathway is critical for hippocampal memory, however the role of neuropeptide signaling between these subfields in plasticity and learning remains less clear. While previous work has identified pro-opiomelanocortin (POMC)-expressing neurons in CA3 and corresponding melanocortin 4 receptor (MC4R)-expressing neurons postsynaptically in CA1 and found activation of the pathway ameliorates cognitive deficits in a mouse model of Alzheimer's disease, the role of this circuit in normal hippocampal memory remains poorly understood. Here, we investigated the role of this POMC/MC4R circuit in the hippocampal-dependent Novel Object Recognition Task (NORT), a well-established assay that exploits rodents' innate preference for novelty. Genetic inhibition of neuropeptide release from CA3 POMC neurons reduced novel object preference compared to control mice. Similarly, systemic administration of an MC4R antagonist reduced novel object preference compared with saline-treated animals. Fiber photometry recordings revealed the temporal relationship between specific neuropeptide related activity and behavioral performance. Together, these findings suggest that POMC signaling from CA3 neurons to MC4R-expressing neurons in CA1 contributes to hippocampus-dependent recognition memory and may represent a novel neuromodulatory mechanism underlying cognitive function.

Disclosures: E. Tominaga: None. **Y. Zhou:** None. **T.J. McHugh:** None.

Poster

PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.16/LL51

Topic: I.08. Learning and Memory

Support: NIA Grant AG028084
State of Arizona
Arizona Alzheimer's Consortium
NIH Alzheimer's Disease Research Center P30AG019610
Arizona Department of Health Services ADHS14-052688

Title: Removed but Not Forgotten: Investigating the Age-Dependent Cognitive Effects of Hysterectomy in a Female Rat Model

Authors: *M. W. OEVERMANN[1,3], S. A. CORBIN[1,3], R. T. DOYLE[1,3], J. A. PASTOR[1,3], C. R. LIZIK[1,3], E. S. WU[2], H. A. BIMONTE-NELSON[1,3];

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Abstract: Hysterectomy, the surgical removal of the uterus, is the most common gynecologic procedure in the United States, with 22% of U.S. women over the age of 45 undergoing the procedure. Despite non-invasive alternatives for some benign indications, hysterectomy persists and can occur during any stage of a woman's life, spanning young adulthood to postmenopause. Research has shown that hysterectomy with ovarian retention increases dementia risk, a finding that is exacerbated when surgery occurs at younger ages, implicating surgery age as a variable of interest. We have shown analogous findings, with impairments to spatial working memory in young hysterectomized rats extending to one year after surgery. Currently, no preclinical work has evaluated age at hysterectomy as a variable of interest, with a focus of surgery in late adulthood. The present study aimed to address this research gap by administering hysterectomy to groups in either young or aged timeframes, thereby directly assessing whether cognitive impacts of hysterectomy differ by age at initiation. Young and aged female rats from the NIA colony were randomly assigned to receive either Sham-control surgery or Hysterectomy. Vaginal smears were assessed to confirm estrous cyclicity following surgery. A behavior battery was used and included the water radial-arm maze, the Morris water maze, and the delayed-match-to-sample plus maze to examine impacts to spatial short-term, working, and reference memory. Next, the visible platform task was used to examine competencies of visual, motoric, and water-maze procedural components. Aging resulted in deficits in both Sham and Hysterectomy groups, with aged rats making more errors compared to young rats for each surgery type, for each behavior tasks. Hysterectomy yielded deficits to both spatial working and reference memory. All rats successfully completed the visible platform task indicating competence of procedural water-maze performance and expected vaginal smear cyclicity statuses were noted for all groups with no differences between sham and hysterectomy rats within each age cohort. The current study demonstrates broad age-related decreases in performance across multiple memory domains, and that detrimental effects of hysterectomy occur regardless of if surgery occurs during young or aged timeframes, with effects not due to issues in motoric, visual, or procedural components. This research replicates and extends our prior findings of hysterectomy and adds to the growing scientific landscape actively overturning prior dogma by asserting the non-pregnant uterus is indeed involved in factors beyond reproduction, including but not limited to cognition.

Disclosures: M.W. Oevermann: None. **S.A. Corbin:** None. **R.T. Doyle:** None. **J.A. Pastor:** None. **C.R. Lizik:** None. **E.S. Wu:** None. **H.A. Bimonte-Nelson:** None.

Poster

PSTR381: Hippocampal-Entorhinal Circuit Mechanisms of Memory: Ripples, Replay, and Neuromodulation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR381.17/LL52

Topic: I.08. Learning and Memory

Support: NIH Alzheimer's Disease Research Center P30AG019610
Funding support provided through the Opportunity Through Entrepreneurship Foundation AZAdvances Initiative

Title: The cognitive effects of nonhormonal menopausal therapy depend on the presence of the reproductive tract organs: Exploring the new horizon of vasomotor therapies

Authors: *C. R. LIZIK, K. J. ANYIGBO, E. S. WU, M. W. OEVERMANN, R. T. DOYLE, S. A. KALAS, A. GARAYZAR LOPEZ, I. GONZALEZ-CRUZ, M. K. HANNAHS, I. KAUR, H. A. BIMONTE-NELSON;
Arizona State Univ., Tempe, AZ

Abstract: Within the last several years, new nonhormonal pharmacotherapies targeting the neurokinin (NK) system have been developed for the treatment of menopausal-associated vasomotor symptoms (VMS), which include hot flashes and night sweats. The NK system plays a role in thermoregulation, and NKR antagonists are considered a safe alternative to hormonal formulations often used for menopausal therapy. The implications of NKR antagonism on cognition are not well understood, but are especially relevant considering that the majority of users are menopausal women, who are at increased risk for the development of Alzheimer's disease (AD). Moreover, approximately half of women experience gynecological surgery with reproductive tract organ removal in their lifetime, highlighting the need to understand the effects of a range of menopausal therapies on gynecological tract variants. Here, we used a rodent model to evaluate the impact of Fezolinetant (Fez), a recently approved NKR antagonist used for VMS, on cognition across several models of gynecological surgery: Ovariectomy (removal of the ovaries with uterine retention, Ovx) and Hysterectomy (removal of the uterus with ovarian retention, Hyst), as well as in sham-operated controls. Fez improved memory performance in sham-operated, reproductively-intact rodents, an effect not seen when any part of the reproductive tract was removed. This is the first report suggesting that Fez improves memory, and that this mnemonic functional impact is altered by gynecological surgery. These outcomes have far-reaching implications; indeed, as evidence is accumulating, our understanding is evolving and supporting the tenet that menopause is not a singular process or physiological event. There are distinct variations in how individuals experience menopause, underscoring the importance of individualized medicine, including varied evaluative and therapeutic approaches. This study, combined with evidence that less than 3% of neuroscience research is devoted to women’s health-related factors, underscores the critical need to further investigate how menopause therapies impact multi-systems health, especially when mapped onto varied backgrounds of menopause and reproductive tract status. More focus in this research domain is needed so that targeted, personalized therapeutic strategies for menopause can be developed to optimize brain health during aging in women and gender-nonconforming individuals.

Disclosures: C.R. Lizik: None. **K.J. Anyigbo:** None. **E.S. Wu:** None. **M.W. Oevermann:** None. **R.T. Doyle:** None. **S.A. Kalas:** None. **A. Garayzar Lopez:** None. **I. Gonzalez-Cruz:** None. **M.K. Hannahs:** None. **I. Kaur:** None. **H.A. Bimonte-Nelson:** None.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.01/LL53

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

Title: D55, a novel apomorphine derivative, exhibits improved pharmacokinetics compared with apomorphine in mice

Authors: *K. NAGAI[1], N. KIMURA[2], T. ISHIMA[3], H. OSAKA[5], K. AIZAWA[4];
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Abstract: Apomorphine has traditionally been used to treat off episodes in Parkinson's disease; however, recent studies have demonstrated that it exhibits anti-cell death activity in patient-derived cells with mitochondrial disease, including Leigh syndrome; however, its short half-life (~ 30 minutes) has been a limitation. D55 is a novel apomorphine derivative that lacks dopaminergic activity and exhibits stronger anti-cell death effects than apomorphine in mitochondrial disease patient-derived cells. To support future preclinical studies for mitochondrial diseases, this study aimed to establish a quantitative analytical method for D55 and characterize its pharmacokinetics in mouse plasma. A sensitive and selective liquid chromatography-tandem mass spectrometry method was developed to quantify D55 and apomorphine. Apomorphine-d_5 was used as an internal standard. Compounds were separated on a C18 column and detected using multiple reaction monitoring in positive electrospray ionization mode (D55: m/z 296.0 -> 189.2; apomorphine: m/z 268.0 -> 219.2; apomorphine-d_5: m/z 273.1 -> 241.3). Calibration ranges were 0.92-14.8 ng/mL for D55 and 0.83-26.7 ng/mL for apomorphine. For pharmacokinetic analysis, mice (n = 5) received a single subcutaneous dose (0.5 mg/kg), and plasma samples were collected over time and analyzed. All animal procedures were approved by the Institutional Animal Care and Use Committee of Jichi Medical University. Data are presented as mean ± standard deviation. The method showed good accuracy and precision, with intra- and inter-day accuracy of 86.9-108.6% and precision < 9.77% for D55, and 99.2-104.5% and < 7.52% for apomorphine. D55 exhibited a 3.13-fold longer plasma half-life than apomorphine (78.4 ± 16.1 vs. 24.9 ± 4.7 min, two-way ANOVA, $p < 0.0001$). The plasma area under the curve of D55 was 2.60-fold greater than that of Apomorphine (8739 ± 1173 vs. 3394 ± 748 min·ng/mL), indicating increased systemic exposure. The improved pharmacokinetic profile of D55 is likely related to its molecular structure. D55 is an apomorphine derivative in which the hydroxyl group at the 10-position is replaced by an ethoxy group. This modification increases lipophilicity and may reduce metabolic susceptibility, potentially decreasing clearance and prolonging half-life. D55 demonstrates prolonged pharmacokinetics compared to apomorphine, suggesting potential for sustained therapeutic effects and supporting its development as a candidate for mitochondrial diseases.

Disclosures: K. Nagai: None. **N. Kimura:** None. **T. Ishima:** None. **H. Osaka:** None. **K. Aizawa:** None.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.02/LL54

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

Support: FI21/000919
MS19/00200
PI23/00496
PID2021-127800OA-I00

Title: Noninvasive focal gene delivery into the cerebellum of non-human primates using focused ultrasound

Authors: N. ESTEBAN-GARCÍA[1,2], J. A. PINEDA-PARDO[1], I. TRIGO DAMAS[1], M. GUTIÉRREZ FERNÁNDEZ[3], M. CASTILLO[1,4], M. CARRILLO DÍAZ[5], A. REINARES SEBASTIÁN[5], V. MEDINA CHAVARRÍAS[1], M. TAKADA[6], J. A. OBESO[1], *J. BLESA[1]; [1]Fundación de Investigación HM CINAC, Madrid, Spain; [2]PhD Program in Neurosci., Autónoma de Madrid University-Cajal Inst., Madrid, Spain; [3]Fundación de Investigacion HM CINAC, Madrid, Spain; [4]PhD Program in Technologies for Hlth. and Well-being, Polytechnic Univ. of Valencia, Valencia, Spain; [5]CIBER – Ctr. de Investigación Biomédica en Red Inst. de Salud Carlos III, Madrid, Spain; [6]Neurol., OSAKA UNIVERSITY, Suita, Osaka, Japan

Abstract: Cerebellar degenerative disorders comprise a diverse group of conditions that represent a growing clinical challenge, as no disease-modifying therapies are currently available to prevent or slow their progression. Gene therapy has emerged as a promising approach for the treatment of neurological diseases; however, its clinical application remains limited by major delivery constraints, most notably the blood-brain barrier (BBB), which severely restricts the systemic access of therapeutic vector to the brain, particularly in primate species. Overcoming this obstacle is therefore critical for the successful translation of gene-based interventions. In this study, we investigated the use of low-intensity focused ultrasound combined with intravenously administered micro bubbles as a non-invasive strategy to transiently open the BBB in the cerebellum of adult macaque monkeys. This approach was employed to facilitate targeted delivery of adeno-associated virus (AAV)-based gene therapy vectors following systemic administration. Two distinct vector configurations, self-complementary and single-stranded AAVs, were evaluated to compare transduction efficiency and cellular tropism within the cerebellum. Focused ultrasound-mediated BBB opening enabled precise, localised gene delivery to the cerebellum without the need for intracranial injections. Both vector types successfully reached the targeted region, displaying differential transduction patterns: one vector predominantly transduced neuronal populations, whereas the other showed preferential expression in glial cells. Notably, a single intravenous administration of the single-stranded AAV vector combined with focused ultrasound resulted in robust and widespread transduction of neurone within the targeted deep cerebellar nuclei. Collectively, these findings demonstrate the

feasibility and effectiveness of focused ultrasound-assisted BBB opening as a minimally invasive platform for cerebellar gene delivery in non-human primates. This strategy holds strong translational potential for the development of gene therapies targeting cerebellar and other neurodegenerative disorders.

Disclosures: N. Esteban-García: None. **J.A. Pineda-Pardo:** None. **I. Trigo Damas:** None. **M. Gutiérrez Fernández:** None. **M. Castillo:** None. **M. Carrillo Díaz:** None. **A. Reinares Sebastián:** None. **V. Medina Chavarrías:** None. **M. Takada:** None. **J.A. Obeso:** None. **J. Blesa:** None.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.03/LL55

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

Title: Root-Cause Analysis of Magnetic Resonance Imaging (MRI)-Guided Intracerebroventricular Mistargeting in the Non-Human Primate at a Preclinical Contract Research Laboratory

Authors: S. WOODS, J. J. DEVRIES, J. OGLE, J. HORVATH, S. WILSON, D. LINIHAN, ***B. GUNTER**;
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Abstract: Delivery of therapeutics with central nervous system (CNS) indications that cannot readily cross the blood brain barrier require a surgical approach. Intracerebroventricular (ICV) drug delivery to the lateral ventricle has been shown previously to provide improved distribution within the brain compared to other routes of administration (intrathecally via the intracisternal magna and lumbar cistern). While the stereotactic atlas is utilized for ICV drug delivery in rodents, it is more common to use MRI-guided delivery for ICV in large animals due to animal-animal variability in skull and brain anatomy. At Charles River Laboratories, the large animal species that is typically selected for ICV studies is the non-human primate (NHP) due to its similarities of anatomic structures in the human central nervous system. The animal is placed in an MRI-compatible stereotactic frame, imaged via MRI, uploaded to the OsiriX MD targeting software, and the coordinates are calculated based on the measurements garnered from the MRI. Placement of a spinal needle into the lateral ventricle based on the coordinates is confirmed via contrast injection viewed with fluoroscopy. Following confirmation, test articles can be administered through the needle. This workflow had been successful in many animals until needle placement in the ventricle(s) could not be confirmed on several occasions. This necessitated a root-cause analysis of the underlying issue such that the error in coordinate calculations could be rectified and therefore the capability could be offered to sponsors without hesitation. There are several steps in the procedure that were investigated: the frame and device arms, the targeting software, and the MRI protocol utilized. After a thorough investigation of

each, it was determined that the MRI protocol had been adjusted such that the third ear bar used for sagittal plane alignment was not in the frame of view and the scanning parameters were based on lateral ventricle alignment instead of the ear bars. Once the adjustments were made to both workflow steps, successful ICV targeting of multiple animals was confirmed via fluoroscopy. This successful root-cause analysis restored confidence in the MRI-guided ICV delivery workflow at Charles River Laboratories and highlighted the sensitivity to seemingly minor protocol changes.

Disclosures: S. Woods: A. Employment/Salary (full or part-time):; Charles River Laboratories. **J.J. DeVries:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **J. Ogle:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **J. Horvath:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **S. Wilson:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **D. Linihan:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **B. Gunter:** A. Employment/Salary (full or part-time):; Charles River Laboratories.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.04/LL56

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

Title: polyNaut: non-viral, targeted polymer nanovesicles for cell-specific targeting across the blood-brain barrier

Authors: N. KOULI, K. WU, M. MARCHETTI, P. VILELA, E. BOTTARO, R. MARROCCELLA, T. KONSTANTINOU, *P. MANJAPPA, A. BAHREMAN, A. SIKDER, L. PRATT, M. MASCELLONI, **S. WYTHE**, D. CECCHIN, R. JUPP;
ViaNautis Bio Ltd, Cambridge, United Kingdom

Abstract: A major bottleneck in the development of genetic medicines for central nervous system (CNS) disorders is efficient systemic delivery across the blood-brain barrier (BBB). Viral vector-based approaches have been extensively investigated but face challenges around transcytosis efficiency, cargo capacity, and safety; while non-viral approaches for systemic BBB crossing are still emerging. Here, we present polyNaut, a versatile, disease-agnostic targeted polyNaut nanovesicle (tPNV) platform, designed to enable a plug-and-play approach for precise cell- and tissue-specific targeted delivery. Systemically administered tPNVs have the potential for delivering precisely targeted, safer and redosable gene therapies for CNS disorders.
A tPNV has three key components: a single type of block co-polymer, a genetic cargo and a nanobody for targeting a defined cell surface receptor. Block co-polymers undergo polymerisation to self-assemble into a polyNaut nanovesicle (PNV). Nanobodies are conjugated to the surface of the assembled PNV to form a targeted PNV (tPNV), such that they target specific cell populations via receptor-mediated nanobody binding.

To select tPNVs with optimal BBB transcytosis, we designed and formulated a suite of 15 CNS-tPNVs conjugated with different CNS-targeting nanobodies, covering a range of binding affinities and surface densities. Following intravenous administration of CNS-tPNVs into mice, the in vivo binding of CNS-tPNVs to the brain vasculature, transcytosis and cellular uptake were evaluated using in vivo imaging system (IVIS) and immunohistochemistry. Dose-dependent brain uptake of CNS-tPNVs was observed, with evidence of neuronal and astrocytic internalisation across the forebrain, midbrain and hindbrain regions. Functional delivery by CNS-tPNVs was subsequently evaluated in relevant models.
With simple, scalable manufacturing and no immunogenicity or inflammation observed, CNS-tPNVs present a potential solution for delivering safer, redosable and precisely targeted gene therapies for CNS disorders with high unmet needs.

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Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.05/LL57

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

Support: R03MH135358
P20GM103395

Title: Non-invasive brain delivery of functional siRNA by an alpha7 nicotinic acetylcholine receptor-selective nanoparticle delivery system

Authors: B. C. OBRIEN, L. WEBER, ***M. M. WELTZIN**;
Chem. and Biochem., Univ. of Alaska Fairbanks, Fairbanks, AK

Abstract: Cell-penetrating peptides (CPPs) are an attractive therapeutic avenue due to their ability to deliver molecular cargo into the central nervous system (CNS) by peripheral administration, but are hindered by a lack of selectivity for specific cellular macromolecules. This broad tropism restricts their utility, as neurological diseases typically target specific proteins and pathways within distinct cellular populations. CPPs derived from the rabies virus glycoprotein (RVG) can access the CNS by binding to plasma membrane targets, including, but not exclusively, nicotinic acetylcholine receptors (nAChRs). To overcome this limitation, our lab integrated regions of a naturally alpha7 nAChR subtype-selective protein to create the neurotropic nanoparticle drug delivery system, ARA22. Major depressive disorder is associated with hypercholinergic tone driven in part by the alpha7 subtype and decreased brain-derived neurotrophic factor (BDNF) in the hippocampus. Decreased BDNF expression is further

accompanied by a concomitant increase in the protein translational repressor programmed cell death 4 (PDCD4). We hypothesized that by complexing silencing RNA (siPDCD4) to ARA22, we could engineer a potential therapy that alters PDCD4/BDNF mRNA levels in alpha7 nAChR-expressing cells. Using human-induced pluripotent stem cell-derived glutamatergic neurons, we demonstrated that ARA22 requires surface expression of the alpha7 nAChR to internalize and successfully deliver fluorescent nucleic acid cargo into the neuronal cytoplasm. RT-qPCR analysis revealed that while ARA22 or RVG treatments had no significant effect on PDCD4, ARA22 did induce a robust upregulation of BDNF transcripts. To establish a translational model with an intact blood-brain barrier (BBB), C57BL/6J mice received intraperitoneal injections of siRNA complexed with ARA22 or RVG, or 5% glucose (vehicle). Immunohistochemical analysis revealed elevated fluorescence intensity in the alpha7 nAChR-enriched hippocampus, confirming successful brain delivery, with improved transport efficiency noted for ARA22. To evaluate the functional efficacy of the delivered cargo, mice were injected with either non-coding siRNA or siPDCD4 complexed to RVG or ARA22 (~6 per group/sex). RT-qPCR was performed on hippocampus and prefrontal cortex samples. Interestingly, we observed a sex difference: ARA22 successfully upregulated BDNF mRNA transcripts in females but not in males. Collectively, our alpha7 nAChR-targeted nanoparticle delivery platform offers research and translational utility as a non-invasive strategy to escort therapeutic cargos, such as siRNA, across the BBB.

Disclosures: B.C. OBrien: None. **L. Weber:** None. **M.M. Weltzin:** None.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.06/LL58

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

Support: RS-2024-00402116
RS-2024-00419358
RS-2024-00415957

Title: Development of a Dexamethasone-Eluting Cochlear Implant Platform: Characterization and In Vitro Evaluation

Authors: *Y. PARK[1], S. LEE[1], K. MIN[4], S. JUN[1,2,3];
[1]Dept. of Electronic and Electrical Engin., [2]Div. of Brain & Cognitive Sci., [3]Ewha Brain Inst., Ewha Womans Univ., Seoul, Korea, Republic of; [4]TODOC, Seoul, Korea, Republic of

Abstract: Cochlear implants (CIs) are widely used neural prosthetic devices for auditory rehabilitation in patients with severe-to-profound sensorineural hearing loss. However, inflammatory responses and fibrotic tissue formation induced during electrode insertion may compromise the stability of the electrode-tissue interface and negatively affect long-term

auditory performance. To address these challenges, drug-eluting electrode technologies that enable localized delivery of anti-inflammatory agents have emerged as a promising strategy for improving cochlear implant outcomes. Dexamethasone (Dexa), a potent corticosteroid with strong anti-inflammatory properties, has been extensively investigated for its ability to suppress intracochlear inflammation and reduce tissue responses associated with cochlear implant electrodes. In this study, a Dexa-eluting cochlear implant system is being developed using silicone elastomer as a drug reservoir, and its drug release characteristics are being evaluated to assess its potential as a localized drug delivery platform. In parallel, microglia-based in vitro inflammation models are being used to evaluate the biological efficacy and anti-inflammatory effects of Dexa. By combining the characterization of Dexa release with the evaluation of its biological efficacy, this study aims to provide fundamental insights into the development of Dexa-eluting cochlear implant electrodes and to support future strategies for localized anti-inflammatory drug delivery in cochlear implant applications.

Disclosures: Y. Park: None. **S. Lee:** None. **K. Min:** None. **S. Jun:** None.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.07/LL59

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

Title: A novel liver de-targeted blood-brain barrier penetrant AAV capsid robustly transduces the CNS while minimizing transduction of peripheral tissues

Authors: *J. B. SMITH, B. P. HEITHOFF, E. FIRNBERG, S. YOST, S. TEJADA, T. CHEN, H. JASICK, S. SMITH, C. PETERSEN, T. NGUYEN, Y. LIU, O. DANOS;
REGENXBIO, Inc., Rockville, MD

Abstract: Recent advances have improved the ability of adeno associated viral vectors (AAVs) to cross the blood brain barrier (BBB) at lower doses than naturally occurring serotypes such as AAV9, allowing intravenous delivery of therapeutic AAV gene therapies. By targeting known BBB shuttles, such as the transferrin receptor 1 (TfR1), we identified peptide insertions in the VR-VIII loop of AAV9 that enable TfR1 binding and allow for greater BBB penetrance. However, transduction of peripheral tissues, such as the liver, remain quite high, potentially yielding off-target challenges. Here, we present a novel capsid that efficiently crosses the BBB while also de-targeting peripheral organs to achieve maximum expression in the CNS with negligible off-target transduction.
Utilizing REGENXBIO's proprietary directed evolution platform, *NAVIGATE*, we identified a novel VR-VIII peptide insertion that binds the human transferrin receptor (hTfR1) that can be combined with additional capsid mutations to de-target the liver and other peripheral tissues. Three weeks after IV injection of AAV.BBB.P2 at 5e13 GC/kg into humanized-TfR1knock-in mice, we found broad, robust transduction in the CNS. Vector DNA biodistribution assessed by

ddPCR was 50x higher in the brain (~30 GC/cell) and 175x higher in the spinal cord (~90 GC/cell) compared to wild-type AAV9 levels at the same dose (<1.0 GC/cell). Remarkably, vector DNA in the liver was >2,000x lower than AAV9, yielding an average of <0.1 GC/cell for AAV.BBB.P2. Similarly, biodistribution in heart was <1.0 GC/cell and skeletal muscle was <0.1 GC/cell. Analysis of mRNA transcripts for tdTomato followed these trends. Histological processing revealed that AAV.BBB.P2 broadly transduces the CNS, with robust expression observed throughout the entire cortex (particularly layer 5 pyramidal neurons), hippocampus, thalamus, and striatum. We further characterized AAV.BBB.P2 at a wider range of doses including 5e12, 1e13, and 1e14 GC/kg, as well as performing single nucleus RNAseq (snRNAseq) on whole brain hemispheres to assess the cell-type specific transduction profile. These results demonstrate that AAV.BBB.P2 achieves significantly reduced off-target expression while maintaining efficient CNS transduction, yielding 300x greater vector biodistribution in brain compared to liver and skeletal muscle. This novel AAV capsid achieves unprecedented tissue specificity in the brain, ideal for non-invasive gene transfer to the CNS with the potential to treat a wide range of neurologic diseases.

Disclosures: J.B. Smith: A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **B.P. Heithoff:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **E. Firnberg:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **S. Yost:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **S. Tejada:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **T. Chen:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **H. Jasick:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **S. Smith:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **C. Petersen:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **T. Nguyen:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **Y. Liu:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **O. Danos:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc..

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.08/LL60

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

Title: Procedural technique comparison for intracerebroventricular administration in mice with histopathology evaluations

Authors: *D. LINIHAN[1], J. J. DEVRIES[1], B. GUNTER[1], S. WILSON[1], S. CARON[2], C. VOYER[2], G. QUESSEVEUR[3], J. MORRISON[4], S. CINQUINO[2];
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Abstract: The development of therapeutic modalities for central nervous system (CNS) disorders, including gene and cell therapies, oligonucleotide-based approaches, and other

therapeutic agents, represent a promising strategy for treatment. However, clinical success has been limited due to the physiological challenges associated with transport across the blood brain barrier. There is an additional concern of off-target gene expression and potential immunological responses when these therapies are delivered systemically. Therefore, it is necessary to develop and refine surgical procedures to safely deliver these therapies into the target tissue of interest. Intracerebroventricular (ICV) administration in mice is a common high throughput model to evaluate early toxicity of therapies targeting the CNS. This is a standard procedure routinely performed across multiple Charles River discovery and safety assessment (DSA) sites. The procedure uses stereotaxic coordinates derived from the standard mouse atlas ensuring high reproducibility. In the interest of procedural refinements and the 3Rs principles, recent technological advancements such as microsurgical drills have enabled improvements to the standard mouse ICV delivery methods previously adopted at Charles River. For example, performing a craniotomy vs a direct needle puncture through the skull represents one such potential refinement. Additionally, differences in formulation properties, such as increased viscosity of some therapies (e.g. cell therapies) may require the use of a larger gauge needle for administration, whereas other therapies may require a slow infusion as opposed to the standard bolus injection. Charles River conducted a study in C57BL/6 male mice of at least 21 days old to evaluate the potential impact of different surgical techniques and procedural variations on early toxicity assessment and histopathology findings. Parameters that were assessed included comparing craniotomy vs direct needle entry, needle gauge, and slow bolus injection at 1 µL/second vs. slow infusion at 2 µL/minute. Animals were randomized into different surgical technique groups, then euthanized on Day 1 or recovered from surgery and euthanized on Day 5. Histopathology slides were generated from brain, spinal cord, and any macroscopic abnormalities, stained with hematoxylin and eosin (H&E), and evaluated by a board-certified pathologist. The results of this study demonstrated that there were no meaningful differences in the incidence and/or severity of microscopic findings between surgical approaches (craniotomy vs. direct needle puncture) across techniques, needle gauge, or infusion rates.

Disclosures: D. Linihan: A. Employment/Salary (full or part-time):; Charles River Laboratories. **J.J. DeVries:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **B. Gunter:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **S. Wilson:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **S. Caron:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **C. Voyer:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **G. Quesseveur:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **J. Morrison:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **S. Cinquino:** A. Employment/Salary (full or part-time):; Charles River Laboratories.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.09/LL61

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

Support: NIH Maximizing Investigators' Research Award (MIRA) Grant (R35GM147408)
National Science Foundation (NSF) CAREER award (2340964)

Title: Intravenous infusion of ultrasound-cleavable, hydrogen-bonded nanoparticle system enables spatiotemporally precise delivery of neurotherapeutics for minimally invasive neuromodulation

Authors: *B. ARTMAN, B. SHRESTHA, K. TANG, F. HARLEY, S. MEJIA, K. KIM, W. HE, T. PORTER, H. WANG;
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Abstract: Despite advances in biased agonism for receptor-specific neuropharmacology, a given receptor is often represented in multiple subregions throughout both the central and peripheral nervous systems, thereby producing off-target side effects that often narrow the therapeutic range. While direct injections can circumvent this issue, minimally invasive alternatives are needed to avoid the high-risk surgeries and physical trauma associated with injecting into brain tissue. Focused ultrasound (FUS), when paired with intravenously (IV) infused, lipid-stabilized microbubbles (MBs), has enabled non-invasive and transient blood-brain-barrier (BBB) permeabilization, allowing circulating BBB-impermeable pharmaceuticals to penetrate brain tissue. However, the other organs are still exposed to these systemically administered drugs. To address this challenge, we intravenously co-administered MBs with our previously reported hydrogen-bonded organic frameworks (HOFs; Wang et al., 2025) into the tail vein of male C57Bl/6 mice (5-6 weeks old) to enhance the spatiotemporal precision of small molecule delivery to the brain. After first pre-opening the BBB at contralateral regions of the primary motor cortex with MBs and brain atlas-guided stereotaxic burst FUS, we were able to compare contralateral differences in BBB-impermeable dye delivery following exposure to a second, custom compound FUS waveform that combines a lower power HOF/MB collection phase and a higher power drug uncaging phase. Against the within-group contralateral controls and between-group subtractive controls (n=4), we have shown that the combination of compound FUS, MBs, and dye-loaded HOF produced the largest contralateral improvement (57% increase over ‘no FUS’ control, $p < 0.05$, one-way ANOVA) in dye delivery in a FUS pressure-dependent manner. Next, to demonstrate neurophysiological responses, we loaded our HOF with 3,4-diaminopyridine (3,4-DAP), a representative BBB-impermeable and FDA-approved potassium channel blocker. We then aimed the FUS at the dorsolateral striatum and piriform cortex and fixed the brain tissue after 90 minutes to evaluate comparative c-fos expression. Against the same subtractive controls (n=4), we found that c-fos expression increases when 3,4-DAP is loaded into the HOF. Because our HOF nanoparticles have been loaded with many classes of drugs, both permeable and impermeable to the BBB, we expect these results to represent a novel merging of high drug loading capacity with on-demand, non-invasive, and spatiotemporally precise release to target brain regions for a wide variety of pharmacotherapeutics.

Disclosures: B. Artman: None. **B. Shrestha:** None. **K. Tang:** None. **F. Harley:** None. **S. Mejia:** None. **K. Kim:** None. **W. He:** None. **T. Porter:** None. **H. Wang:** None.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.10/LL62

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

Support: CBF-2025-G-1274

Title: Pharmacological activation of the neurotrophin receptor TrkB protects against sucrose-induced testicular oxidative stress and sperm dysfunction

Authors: *T. G. OSORIO PÉREZ[1,2], E. PÉREZ[1], R. JULIO CÉSAR[3], A. CARRASCO CARBALLO[4], F. CASTELÁN[5], J. AGUILERA[6], L. NICOLAS[1];
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Abstract: Brain-derived neurotrophic factor (BDNF) activates tropomyosin receptor tyrosine kinase B (TrkB), producing protective antioxidant effects against neurodegeneration. BDNF-TrkB signaling is identified in the testis, where it mediates communication between Sertoli cells (SCs) and spermatogonia. XT1, a TrkB agonist, has been shown to improve neuronal survival, proliferation, and antioxidant defenses. Our group demonstrated that high sugar intake increases serum testosterone, oxidative stress, antioxidant enzyme activity, testicular cell apoptosis, and lipid droplet accumulation, altering lipid metabolism in SCs and impairing sperm quality. Therefore, this study aimed to investigate whether XT1 attenuates the effects of high sucrose consumption on fertility in young male rats. Twenty-one-day-old male Wistar rats were assigned to three groups (n = 7/group): control (C), 30% sucrose in drinking water (S30), and 30% sucrose in drinking water plus XT1 treatment (S30+XT1). Sugar water was provided ad libitum from postnatal day (PND) 21 to 81. The S30+XT1 group received intraperitoneal injections of XT1 at PND 51 and PND 66 at a dose of 200 µL/kg body weight. Body weight, food intake, and water consumption were recorded daily. At the end of the experiment, the rats were euthanized, and serum was obtained for testosterone and triglyceride quantification. The epididymal cauda was used to assess sperm quality. Lipid peroxidation, antioxidant status, and, in the testis only, triacylglycerol content were evaluated in the testis and epididymis. Results showed that high sucrose intake reduced food and water consumption without affecting total caloric intake or body weight gain. It increased serum and testicular triacylglycerol concentrations and gonadal adiposity. It also increased malondialdehyde levels and decreased catalase activity and ferric reducing antioxidant power (FRAP). Epididymal oxidative stress was reduced without altering catalase activity and FRAP, resulting in low sperm quality. Treatment with XT1 prevented the increase in serum triacylglycerols and attenuated testicular oxidative stress by improving catalase activity and FRAP, thus improving sperm quality. In conclusion, chronic sucrose intake affected

sperm quality by inducing testicular oxidative stress and disrupting epididymal homeostasis. Treatment with XT1 mitigated the testicular effects by enhancing antioxidant defenses and preventing hypertriglyceridemia, with TrkB activation proving to be an effective therapeutic strategy for preserving reproductive function. Grant funding SECIHTI; Project number CBF-2025-G-1274.

Disclosures: T.G. Osorio Pérez: None. **E. Pérez:** None. **R. Julio César:** None. **A. Carrasco Carballo:** None. **F. Castelán:** None. **J. Aguilera:** None. **L. Nicolas:** None.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.11/LL63

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

Support: CBF-2025-G-1274

Title: The pharmacological effect of the tetanus heavy chain toxin on the altered metabolic parameters induced by the sucrose intake

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Abstract: In the nervous system, brain-derived neurotrophic factor (BDNF) activates the tyrosine kinase B receptor (TrkB), promoting neuronal survival and antioxidant defense. Its neuroprotective functions and BDNF-TrkB signaling have emerged as regulators of energy metabolism, insulin sensitivity, and glucose homeostasis in peripheral tissues such as adipose tissue. Our group demonstrated that sucrose consumption in rats induces a metabolic syndrome-like phenotype, characterized by adipose tissue expansion, glucose intolerance, insulin resistance, and hypertriglyceridemia. These alterations persist even after sucrose is withdrawn and replaced with plain water, indicating the establishment of long-lasting metabolic dysfunction. The heavy chain of tetanus toxin (TeTx), a TrkB agonist, may represent a novel therapeutic strategy to attenuate these persistent metabolic disturbances. This study aimed to evaluate the effects of TeTx on adipose tissue hyperplasia, glucose tolerance, serum

triglycerides, and insulin resistance in rats after sucrose withdrawal. Twenty-one-day-old male Wistar rats were randomly assigned to three groups (n = 8): control (C), sucrose withdrawal intervention (S30+Int), and sucrose withdrawal plus tetanus toxin heavy chain (S30+TeTx). A 30% sucrose solution was provided ad libitum as drinking water from postnatal day (PND) 21 to PND 81 (60 days). At PND 82, sucrose was withdrawn and replaced with plain water for an additional 60 days. The S30+TeTx group received a single intraperitoneal administration of TeTx (50 µg/kg body weight), and the S30+Int group received saline solution (0.9%, 100 µL), respectively, at PND 111. Body weight, food intake, and water consumption were recorded daily. An oral glucose tolerance test was performed after a 12-hour fast. Subsequently, at euthanasia, serum samples were collected to determine insulin and triglyceride concentrations. Adipose tissue was extracted and weighed. The results presented here correspond to a preliminary analysis of two to three animals per group. Sucrose consumption did not affect body weight, decreased food intake, and increased total caloric intake. Gonadal adipose tissue tended to increase. Treatment with TeTx did not alter any of these variables. Conclusion, the current sample size is insufficient to detect potential metabolic alterations associated with chronic sucrose consumption or TeTx administration. However, the preliminary findings suggest that TeTx does not exert adverse effects on the evaluated metabolic parameters. Grant funding Secretaria de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI); Project number CBF-2025-G-1274.

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Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.12/LL64

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

Title: AI-guided design and highly multiplexed in vivo screening identifies novel shuttles that efficiently deliver therapeutics into the CNS with improved pharmacokinetics, biodistribution and target engagement

Authors: *K. SCEARCE-LEVIE[1], P. ABRAHAMSEN[1], I. ALBUJA[1], F. ANAM[1], J. AVERA[1], M. CASE[1], A. GARCIA[1], A. GEREW[1], H. HADDAD[2], B. K. UNDA[1], N. LIBERMAN-ISAKOV[1], P. OGDEN[1];
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Abstract: Recent Alzheimer's disease therapies have profoundly affected biomarkers associated with disease while delivering mild cognitive benefits. One approach to improve the efficacy and safety of these therapeutics is to facilitate their delivery across the blood-brain barrier (BBB). Technologies relying on the transferrin receptor (TfR1) to exploit receptor-mediated transcytosis have been shown to enhance brain exposure of anti-Aβ antibodies and facilitate plaque removal.

While these approaches have demonstrated meaningful improvements in clinical efficacy, TfR1 is broadly expressed in the periphery as well as the CNS. This creates a large peripheral sink that requires higher doses and the need to engineer the therapeutic to avoid TfR1-related toxicities, including reticulocyte depletion. Alternative BBB receptor targets, or "portals," with differentiated specificity, safety, and potency profiles have the potential to improve delivery for many CNS-targeted therapeutics. Here we describe the discovery and preclinical characterization of shuttles using novel BBB portals to enhance delivery of Alzheimer's disease therapeutics into the CNS.

Our systematic approach to discover novel receptor portals and binders using those portals began by nominating candidate portals with enriched expression on brain endothelial cells. Large combinatorial libraries of binders against these portal targets were generated using AI-guided protein design. Binders were screened in vivo using a proprietary multiplexed platform to assess tissue biodistribution of >500,000 molecules simultaneously in rodents or non-human primates. Binders demonstrating preferential brain enrichment were nominated as shuttle candidates and further characterized with therapeutically relevant payloads.

Constructs of shuttles plus therapeutically relevant monoclonal antibodies (anti-amyloid, anti-tau) or siRNAs (sod1) demonstrated enhanced brain exposures compared to both unshuttled molecules and a TfR1-benchmark shuttle. Shuttling beyond brain vasculature and into brain parenchyma was confirmed by multiple methods, including PK ELISA on capillary-depleted parenchymal fraction, neuronal internalization assays in vitro and in vivo, and payload-specific measures of target engagement. Importantly, these novel shuttles preserved peripheral tolerability with no acute adverse findings.

A combination of AI-guided protein design and high-throughput multiplexed in vivo screening has enabled the identification of novel BBB receptor portals and effective, differentiated shuttles into the CNS at a scale of portal and shuttle evaluation not previously achievable.

Disclosures: K. Scearce-Levie: A. Employment/Salary (full or part-time):; Manifold Bio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Manifold Bio, Denali Therapeutics. **P. Abrahamsen:** A. Employment/Salary (full or part-time):; Manifold Bio. **I. Albuja:** A. Employment/Salary (full or part-time):; Manifold Bio. **F. Anam:** A. Employment/Salary (full or part-time):; Manifold Bio. **J. Avera:** A. Employment/Salary (full or part-time):; Manifold Bio. **M. Case:** A. Employment/Salary (full or part-time):; Manifold Bio. **A. Garcia:** A. Employment/Salary (full or part-time):; Manifold Bio. **A. Gerew:** A. Employment/Salary (full or part-time):; Manifold Bio. **H. Haddad:** A. Employment/Salary (full or part-time):; Manifold Bio. **B.K. Unda:** A. Employment/Salary (full or part-time):; Manifold Bio. **N. Liberman-Isakov:** A. Employment/Salary (full or part-time):; Manifold Bio. **P. Ogden:** A. Employment/Salary (full or part-time):; Manifold Bio.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.13/LL65

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

Title: Overcoming major hurdles in AAV-based ocular gene therapy development

Authors: *C. FERNANDES, C. RICH, S. STORRIE, L. ZHOU, A. LIU, B. LUO, G. YU, B. LAHN;
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Abstract: AAV is widely used in ocular gene therapy development, with one FDA-approved therapy for inherited retinal dystrophy already in use and several candidates in late-stage development. However, no new AAV-based therapies have been approved since 2017, highlighting key challenges that continue to hinder clinical translation. While pre-existing AAV serotypes enable targeting across a broad range of cell and tissue types, efficient delivery to therapeutically relevant sites, including the deep retinal layers, remains difficult. In addition, the restricted cargo capacity of AAV vectors limits the number of potential therapeutic gene targets. To overcome these hurdles in translatability, we employed a multifaceted approach. First, we utilized capsid engineering to generate novel AAV capsid variants capable of efficiently targeting the deep retinal layers in both mice and non-human primates. We then employed promoter engineering to further enhance targeting, achieving robust expression in retinal cone cells. Notably, this novel promoter is also significantly smaller than conventional promoters and bidirectional, thereby enabling more efficient use of AAV's limited cargo capacity. Finally, we developed a split vector system, MegaAAV, to enable the delivery of larger therapeutic genes. Utilizing this system, we achieved robust transgene expression and therapeutic efficacy, demonstrated by restoration of visual function in knockout mice. Overall, we highlight the importance of a multidimensional approach to overcome key translational challenges in next-generation AAV-based gene therapy development.

Disclosures: C. Fernandes: None. **C. Rich:** None. **S. Storrie:** None. **L. Zhou:** None. **A. Liu:** None. **B. Luo:** None. **G. Yu:** None. **B. Lahn:** None.

Poster

PSTR382: Drug Delivery

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.14/LL66

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

Support: NIH grant UM1TR004402

Title: DNA tetrahedra functionalization for siRNA delivery across the in vitro blood-brain barrier

Authors: *G. A. RUDAKOV[1], A. KOKOSA[2], A. DEATON[2], E. FOSTER[2], T. L. KINZER-URSEM[3];

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Abstract: Introduction:
Delivery of therapeutics across the Blood-Brain Barrier (BBB) is the most significant bottleneck in the treatment of neurodegenerative disorders. The Blood-Brain Barrier is a complex structure comprising Blood Microvessel Endothelial Cells (BMEC), astrocytes, pericytes, and neurons, all working together to tightly regulate the transport of non-specific molecules (>0.8nm). Nanomaterials can be an effective solution for delivering therapeutics across the BBB. Among nanomaterials, DNA tetrahedra are particularly suitable chassis for BBB drug delivery due to their programmable multimodal functionality, uniformity in size and shape, exceptional biocompatibility, low cost, and robust assembly.
DNA is hydrophilic, and DNA helices in tetrahedra have a negatively charged backbone. These two factors limit DNA TDN's ability to cross the barrier or deliver the siRNA. To overcome this limitation, we present and compare three TDN functionalization approaches to deliver siRNA and induce RNAi. The first approach, cholesterol anchoring, uses covalently attached cholesterol anchors to DNA to increase the local concentration of miRNA to induce endocytosis. The second approach is DNA TDN functionalization with cationic lipids (DOTMA, DOTAP) to trigger clathrin-mediated endocytosis. The third approach is DNA TDN decoration with cationic polymer DEAE-Dextran acting as a hyperosmolar agent, leading to increased cellular uptake.
Materials and Methods:
We have tested the assembly of our four DNA tetrahedra via PAGE, aggregation via Fluorescence Correlation Spectroscopy, and the delivery efficiency via incubating HBEC-5i cerebral microvascular endothelial cells with the functionalized DNA tetrahedra. Neuro Vascular Units made of BMEC HBEC-5i, astrocytes, pericytes, and microglia, cultured on the same side of a Transwell filter, were also used for the in vitro tests. DNA tetrahedra and siRNA were functionalized with fluorophores, and the DNA tetrahedra anchoring, siRNA delivery, and the RNAi results were investigated via confocal microscopy, PCR, and Western Blot.
Results, Conclusions, and Discussions.
Our results show a significant increase in siRNA delivery and RNAi in theHBEC-5i cells and indicate successful delivery of siRNA into the endothelial cells of an NVU. The most successful approach was using the cationic polymer DEAE-Dextran, showing a significant uptake of siRNA in comparison with naked siRNA, cationica lipids, and cholesterol anchors. Further work will be focused on increasing the depth of the BBB penetration and targeting tau and APOE4 protein expression as well as toxicity evaluation of the functionalization methods used.

Disclosures: G.A. Rudakov: None. **A. Kokosa:** None. **A. Deaton:** None. **E. Foster:** None. **T.L. Kinzer-Ursem:** None.

Poster

PSTR382: Drug Delivery

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR382.15/LL67

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

Support: Supported in part by R01NS093416 (NINDS, NIH)
Supported by the Wilmer core grant (P30EY001765)

Title: GLUT-Initiated Endocytosis Enables Selective Targeting of Hyperexcited Neurons and Transporter-Independent Creatine Delivery

Authors: *N. KALE[1], P. VYAS[3], K. MURUGESAN[4], D. CHERUKARAVEEDU[2], S. KANNAN[5], R. KANNAN[1];
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Abstract: Selective delivery of therapeutics to impaired neurons remains a major challenge because conventional therapy cannot distinguish hyperexcited neurons from healthy neuronal populations. Here, we investigated the mechanism underlying neuronal targeting by a ligand-free glucose dendrimer (GD) platform and evaluated its utility for transporter-independent creatine delivery. Hyperexcited HT-22 neurons and human retinal ganglion cells were used to evaluate uptake and trafficking. GD rapidly and selectively accumulated in hyperexcited neurons, exhibiting ~5-fold greater uptake than hydroxyl-terminated dendrimers and ~13-fold greater uptake than polystyrene nanoparticles. Uptake was significantly enhanced in activated neurons and reduced by GLUT1/3 inhibition, ATP depletion, and clathrin inhibition, indicating a GLUT-initiated, energy-dependent internalization pathway. Surface-restricted Fe_3O_4-GD complexes and reduced membrane GLUT expression supported direct transporter engagement. Following internalization, GD preferentially localized to neuronal mitochondria. To demonstrate therapeutic utility, creatine was conjugated to GD to generate GD-Creatine. *In vivo,* Cy5-GD-Creatine accumulated within the periventricular region and fimbria of CP rabbit kit brains, regions associated with neuroinflammation and neurodevelopmental injury. Unlike free creatine, GD-Creatine uptake was unaffected by inhibition of the creatine transporter, demonstrating transporter-independent neuronal delivery. GD-Creatine reduced NMDA receptor-mediated calcium influx, reduced excitotoxicity and oxidative stress, and increased intracellular creatine availability. These findings identify a previously unrecognized GLUT-initiated neuronal targeting mechanism that exploits the altered state of hyperexcited neurons. This pathway enables transporter-independent therapeutic delivery and establishes glucose dendrimers as a platform for neurological disorders characterized by neuronal hyperactivity and impaired creatine transport.

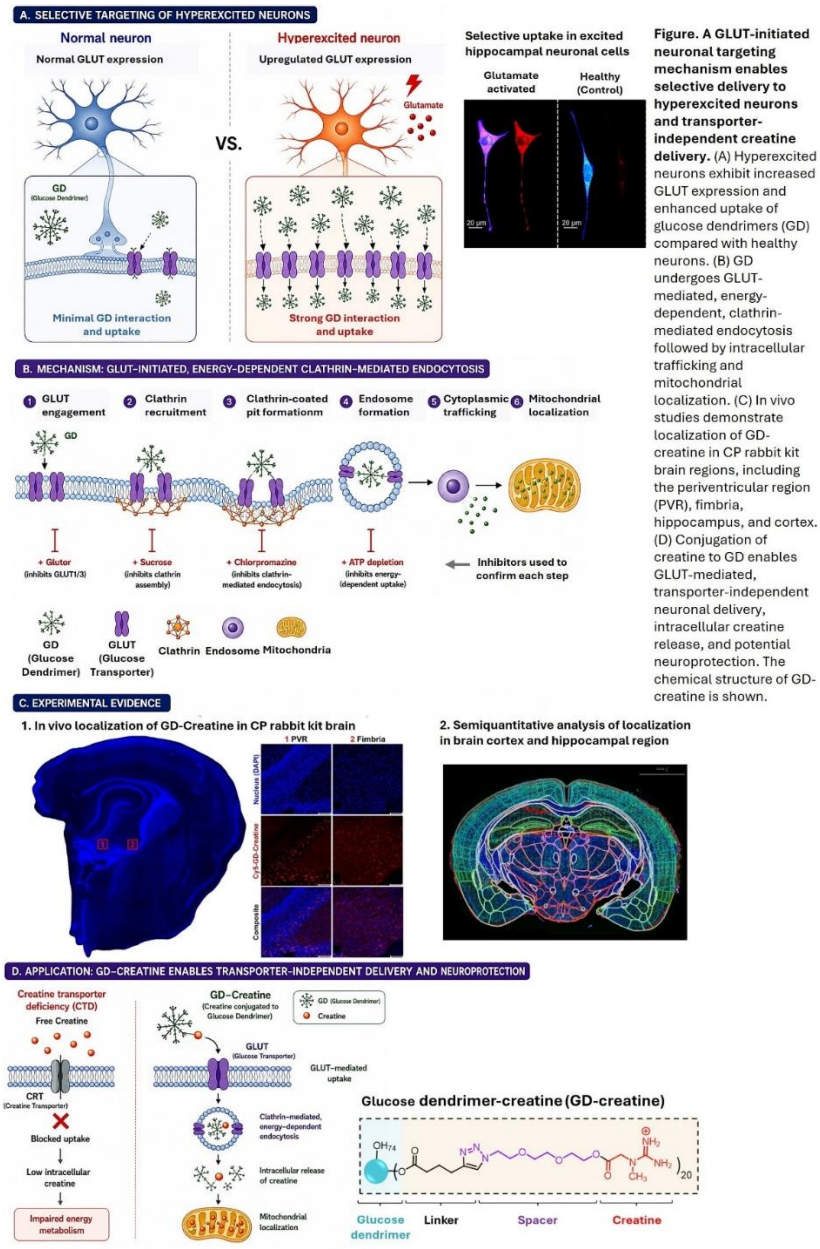


Figure. A GLUT-initiated neuronal targeting mechanism enables selective delivery to hyperexcited neurons and transporter-independent creatine delivery. (A) Hyperexcited neurons exhibit increased GLUT expression and enhanced uptake of glucose dendrimers (GD) compared with healthy neurons. (B) GD undergoes GLUT-mediated, energy-dependent, clathrin-mediated endocytosis followed by intracellular trafficking and mitochondrial localization. (C) In vivo studies demonstrate localization of GD-creatine in CP rabbit kit brain regions, including the periventricular region (PVR), fimbria, hippocampus, and cortex. (D) Conjugation of creatine to GD enables GLUT-mediated, transporter-independent neuronal delivery, intracellular creatine release, and potential neuroprotection. The chemical structure of GD-creatine is shown.

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Poster

PSTR383: Data Analysis: Software Tools I

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR383.01/LL68

Topic: J.07. Data Analysis and Statistics

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Title: Transformer-Based Neural Spike Sequence Analysis Incorporating Anatomical and Activity Properties of Neurons for Cross-Animal Representation Learning

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Abstract: Identifying neural principles that generalize across individuals is a fundamental goal of neuroscience. Recent advances in high-density electrophysiology, such as Neuropixels 2.0, enable simultaneous recording of large neuronal populations. However, the number, identity, and correspondence of recorded neurons differ across animals, making it difficult to directly compare neural activity between subjects. As a result, most existing analyses rely on animal-specific models and primarily capture subject-dependent features rather than shared neural representations. To overcome this limitation, we developed a Transformer-based framework for cross-animal neural representation learning using spike train recordings from the mouse prefrontal cortex obtained with Neuropixels 2.0. Each neuron was characterized by anatomical location and spike-waveform-derived properties, which were incorporated as neuronal metadata. By integrating the temporal modeling capability of POYO with the representation alignment strategy of CEBRA, the proposed model learns neuron-index-independent representations and embeds neural activity from multiple animals into a shared latent space. Application of the model to datasets from multiple mice revealed common neural activity structures across individuals. In particular, activity patterns associated with transitions between wakefulness and sleep were consistently organized within the shared latent space despite substantial differences in recorded neuronal populations. These results indicate that the model captures fundamental neural dynamics shared across animals rather than animal-specific activity patterns. Importantly, the trained model generalized to previously unseen animals without additional training. When applied in a zero-shot manner, neural activity from new subjects was projected into the same latent space and exhibited latent structures comparable to those observed in training animals. This demonstrates that the learned representation is transferable across individuals and is not dependent on a fixed set of recorded neurons. Because the extracted features are shared across animals and remain detectable in novel subjects, they represent promising targets for

experimental causal validation. The proposed framework offers a scalable approach for identifying reproducible and generalizable neural representations from large-scale electrophysiological recordings and may facilitate the discovery of neural features that reflect fundamental principles of brain function rather than individual-specific characteristics.

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Poster

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Support: NIH Grant 1R01MH142410-01
NIH Grant 1U24MH130988-01
CPRIT Grant RP210045

Title: AI agentic networks and large language models for cross-species collaborative annotation of brain cell types

Authors: *W. CHEN[1], R. LI[1], N. S. MAURYA[1], A. SOLANKI[1], M. RAMLAKHAN[1], Z. WU[2], W. ZHENG[1];
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Abstract: Single-cell RNA sequencing (scRNA-seq) has transformed our ability to resolve the cellular diversity of the brain, yet annotating biological function for thousands of transcriptionally defined neuronal and non-neuronal cell clusters emerging from large atlases remains a major bottleneck. Conventional tools such as Gene Set Enrichment Analysis (GSEA) depend on predefined gene sets that are frequently incomplete for brain-specific contexts, and large language models (LLMs), while rich in biomedical knowledge, are limited by hallucinations and weak grounding in structured ontologies. To address this, we developed an open-source, multi-agent AI system that generates reliable, literature-grounded functional annotations for brain cell types across species. We first extracted gene modules from mouse and human whole-brain scRNA-seq atlases generated by the BRAIN Initiative Cell Census Network, grouping genes into co-expression modules based on cell-cell similarity. We then fine-tuned LLMs (Gemma and Llama architectures) separately on curated mouse and human gene sets from the Molecular Signatures Database (MSigDB), each linked to Gene Ontology (GO) terms, teaching principles of biological functions. Retrieval-augmented generation (RAG) grounded predictions in peer-reviewed literature from PubMed to reduce hallucinations and improve interpretability. The system takes gene lists derived from cell clusters and returns consolidated, literature-supported annotations. Performance was evaluated using accuracy and semantic similarity metrics, and domain experts assessed biological relevance.Task-specific fine-tuned models consistently outperformed models without fine-tuning, and across benchmark gene sets.

RAG further improved prediction reliability in both species. Trained and evaluated on over 7,000 gene sets from MSigDB, 77% of mouse and 74% of human sets contained a correct annotation among the top predictions when assisted by the RAG component, exceeding existing LLM-based methods. The system was applied to 5,322 mouse and 3,313 human whole-brain clusters, and it produced biologically meaningful cell-type descriptions and recovered both conserved and species-specific transcriptional programs. It enables novel insights into brain cell function by identifying region-specific gene co-expression patterns. This open, expert-validated resource bridges raw scRNA-seq data and interpretable brain cell-type annotation, reducing manual curation effort and supporting community-driven construction of cross-species brain cell atlases.

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Poster

PSTR383: Data Analysis: Software Tools I

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Program #/Poster #: PSTR383.03/LL70

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant U24NS134536

Title: Pennsieve data analysis at scale: Bridging clinical and scientific workflows through technology

Authors: E. MOYO, A. SWITEK, D. DE FREITAS, J. FROMMEYER, S. KRAFT, M. UFTRING, V. SAMAYAMANTULA, R. SHAH, V. TRUONG, *J. B. WAGENAAR; Univ. of Pennsylvania, Philadelphia, PA

Abstract: Scalable scientific data workflows are increasingly necessary for biomedical research, but many cloud-processing approaches remain difficult for academic labs to adopt because they separate data management from analysis, obscure operational costs, or require researchers to give up control over code, deployment, and reproducibility. A major obstacle to the widespread adoption of many platform technologies is the broad range of requirements and desired features among potential users. Pennsieve was developed eight years ago to address these barriers and now supports data management and integration for multiple large-scale NIH programs, including SPARC, NIH-REJOIN, and the NIH Precision Human Pain Consortium. We continue to extend Pennsieve from a data repository into a sustainable analysis platform that connects clinical and scientific workflows across local and cloud environments.
The platform now provides a framework for scalable, reproducible data processing with native support for distributed compute and storage. This design allows investigators to keep source-controlled applications while deploying analyses close to the data, including workflows that require heterogeneous, or mix-n-match, compute resources such as GPU instances. A central design goal is transparent cost attribution, so that operational expenses can be tracked and

allocated to the users and projects that generate them, making cloud-scale analysis more sustainable for academic research labs. This work paves the way for the next era of scalable and sustainable scientific computing by supporting a broad spectrum of adoption, enabling users to connect existing local workflows, migrate selected analyses to the cloud, or build fully cloud-native pipelines without changing the underlying data governance model.
In collaboration with the Institute for Immunology and Immune Health (I3H), PedQuEST, the NIH BRAIN initiative, BBQS and related communities, we are operationalizing this capability for high-throughput biomedical workflows and generalizing it across Pennsieve's public repository. By integrating distributed compute, scalable storage, provenance-aware deployment, and transparent cost management, Pennsieve lowers barriers to cloud analysis, improves interoperability between compute ecosystems, and enables investigators to perform large-scale analyses without sacrificing control, transparency, or cost efficiency. This work establishes a reusable foundation for large-scale biomedical data analysis that can bridge institutional, clinical, and scientific computing environments leading to accelerated discoveries across shared public data.

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Poster

PSTR383: Data Analysis: Software Tools I

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Topic: J.07. Data Analysis and Statistics

Support: NIH Grant U24NS134536

Title: The Epilepsy Data Ecosystem: Harmonizing Multimodal Human Epilepsy Data for Cross-Site Discovery and Cohort Building

Authors: *D. D. DE FREITAS[1], J. B. BOCCANFUSO[2], Z. ZHOU[1], M. GE[1], V. SAMAYAMANTULA[1], N. SINHA[1], J. B. WAGENAAR[3];
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Abstract: Epilepsy affects over 70 million people worldwide and produces heterogeneous data across imaging, scalp and intracranial electroencephalography (EEG & iEEG, respectively), surgery, outcomes, and clinical records. Cross-site discovery requires infrastructure that makes these data findable, comparable, and combinable, but datasets often remain in lab-specific formats that slow cohort-building and reuse. We present Epilepsy.science, the public entry point for Epilepsy Data Ecosystem (EDE), an open, cloud-based resource that migrates and extends the long-running iEEG.org repository toward harmonized, queryable, multi-site data sharing.

EDE builds on Pennsieve, a scientific data platform that provides scalable storage, FAIR publishing, and a graph-based metadata layer linking files to structured, queryable records. EDE deliberately adopts an opinionated but inclusive data model where files follow the Brain Imaging Data Structure (BIDS) standard with epilepsy-specific conventions for imaging and electrophysiology, while clinical information is captured against Common Data Elements (CDEs), standardized variables with defined permissible values. We curated 1,274 CDEs into 55 reusable bundles and assembled into Case Report Forms through NINDS NT-PRECEDS, enabling prospective studies to produce interoperable data from the start rather than relying on time-consuming retrospective remapping. Structured datasets are stored into the Pennsieve metadata graph and made directly searchable so investigators can assemble cohorts on demand by variables such as intervention type, MRI lesion status, seizure-onset-zone annotation, or surgical outcome. Datasets that do not follow these conventions are still accepted with best-effort metadata extraction, but have reduced discoverability; this creates an incentive for good structure without excluding legacy data. Our EDE resource currently hosts more than 120 public datasets totalling over 23 TB across multiple institutions. Together, these efforts establish a community-owned ecosystem for standardized epilepsy datasets, harmonized clinical metadata, and scalable cloud infrastructure. EDE is designed to support cross-site cohort building, reproducible secondary analysis, and future data driven discovery in human epilepsy research. We actively welcome early-adopter contributors and collaborators on the platform at https://epilepsy.science.

Disclosures: D.D. De Freitas: None. **J.B. Boccanfuso:** None. **Z. Zhou:** None. **M. Ge:** None. **V. Samayamantula:** None. **N. Sinha:** None. **J.B. Wagenaar:** None.

Poster

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Program #/Poster #: PSTR383.05/LL72

Topic: J.07. Data Analysis and Statistics

Support: NIH R24DA064430
NIH U24MH136628

Title: EMBER: NIH BRAIN's Secure, Collaborative Multi-Modal Data Archive for Human and Animal Behavioral Neuroscience

Authors: *N. E. TREGONING[1], R. HINGORANI[1], E. C. JOHNSON[1], L. DIAZ[1], N. THOMAS[1], R. T. HIDER, Jr.[1], C. BAKER[2], N. GUITTARI[1], G. BEZOLD[1], M. PATCHAN[1], M. OGG[1], R. KOWTHA[1], A. EMIKO[1], O. METENKO[4], A. MACDONALD[2], M. SEEBER[8], I. C. TO[2], M. VALLEJO[8], B. PESARAN[5], D. DE FREITAS[4], E. MOYO[4], J. B. BOCCANFUSO[6], J. B. WAGENAAR[7], N. A. SUTHANA[8], D. DUNCAN[4], S. S. GHOSH[9], Y. O. HALCHENKO[3], H. YI[1], B. A. WESTER[1];
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Abstract: NIH BRAIN, through its banner Brain Behavior Quantification and Synchronization (BBQS) program, has pushed the envelope on behavioral neuroscience across human and non-human animal species. As it enters Year 3, the BBQS consortium is at the cusp of generating an unprecedented compilation of high-fidelity data streams for the brain, behavior, and physiology, concurrently collected in complex, dynamic physical and social environments. To foster active collaboration on these data across research teams, paradigms, and model organisms, the BBQS program commissioned the development of the Ecosystem for Multi-modal Brain-behavior Experimentation and Research (EMBER) data archive. EMBER's core infrastructure consists of three main components: (1) an open data sharing platform (EMBER-DANDI) that leverages a crucial piece of BRAIN infrastructure, the DANDI archive, (2) a secure resource for sensitive human data (EMBER-Vault), and (3) a sandbox environment for data staging, exploration, and preprocessing (EMBER-Hearth). EMBER-Vault is a key differentiator from existing neuroscience data archives, providing safeguarded storage for raw human data at the research consortium level, while enabling controlled sharing with vetted and approved researchers. The resource has been intentionally designed to balance data protection with scientific discovery. Sensitive raw human data, such as video and audio recordings directly from sensors, are protected through multiple layers of security, while our data governance strategy promotes reproducibility, enables secondary data use, and supports future discoveries across the research community within the boundaries of established IRB protocols and data-sharing constraints. Specifically, we highlight the following components: (1) authentication and authorization mechanisms, including multi-factor authentication (MFA) and role-based permissions; (2) gated access to the overall resource that combines implementation of NIH-wide policy and other legally binding agreements; (3) repository-specific, granular privilege settings restricted to collaborators who have achieved concurrence through institutional and consortial governance; (4) encrypted file protection during transit and storage. Through hosting multimodal behavior data across species, including secure sensitive human data, and the integration of community developed data analysis and modeling capabilities, EMBER will realize the vision of the BBQS program to promote collaborative research and advance understanding of the neural basis of behavior.

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Poster

PSTR383: Data Analysis: Software Tools I

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Topic: J.07. Data Analysis and Statistics

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NIMH R24 MH117179
NIMH R24 MH11729
NIMH R24 MH136632

Title: STAMPED principles for reproducible research objects in neuroscience

Authors: A. MACDONALD[1], ***C. BAKER**[2], I. C. TO[3], Y. O. HALCHENKO[4];
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Abstract: Neuroscience increasingly depends on the interplay of code, data, and computational environments, yet the record of how they were used together is often incomplete, scattered across repositories, wikis, and notebooks, or lost entirely.This fragmentation undermines rigor, reproducibility, reusability, and efficiency in BRAIN Initiative pipelines that routinely span multiple institutions, archives, and compute platforms.Existing frameworks such as FAIR and FAIR4RS govern discovery and interoperability of digital objects, but do not specify how research objects should be structured and managed so they can be re-executed, extended, and audited.The community lacks a shared vocabulary for this operational layer.
Building on the YODA and VAMP traditions from neuroimaging, and on patterns that have independently converged across geophysics, genomics, statistics, and neuroimaging over three decades, we formalize seven principles a research object should satisfy: Self-containment, Tracking, Actionability, Modularity, Portability, Ephemerality, and Distributability, collectively STAMPED.Each spans a spectrum from practical minimum to aspirational ideal, so adoption is non-prescriptive and incremental.Formal LinkML schemas, an interactive compliance checklist, and the curated collection of examples are provided as enabling tools to this end.
We demonstrate STAMPED through two major neuroscience pipelines.OpenNeuroDerivatives reorganized derivative neuroimaging datasets so they exist as independent Ephemeral units that reference raw inputs as subdatasets rather than nesting under them, removing an upward dependency that previously violated Self-containment, Modularity, and Portability.DANDI Compute, utilizing the Allen Institute for Neural Dynamics electrophysiology pipeline, packages spike-sorting outputs into nested BIDS-derivative units in which each leaf contains the exact code, runtime logs, outputs, and provenance metadata needed to re-execute the analysis, satisfying STAMPED end-to-end.These adoptions show that STAMPED provides a tool-agnostic, incrementally adoptable vocabulary that lets researchers, reviewers, collaborators, and emerging AI agents evaluate and improve the operational maturity of computational neuroscience.By making research objects re-executable and inspectable by construction, STAMPED converts reproducibility from an aspiration into a measurable property of everyday neuroscience practice.

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Poster

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Topic: J.07. Data Analysis and Statistics

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Simons Foundation
The Kavli Foundation

Title: Building Better Data Standards Together: The NWB Enhancement Proposal (NWBEP) Framework and Advances in NWB

Authors: R. LY[1], A. P. BUCCINO[2], S. WEIGL[3], E. HENNESTAD[3], H. MAYORQUIN[3], K. BAKSHI[4], S. E. DE VRIES[2], Y. O. HALCHENKO[5], B. DICHTER[3], ***O. RUEBEL**[1];
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Abstract: Neurodata Without Borders (NWB) is a popular data standard and software ecosystem for neurophysiology and behavioral data. By providing a common language for complex, multimodal experiments, NWB facilitates seamless data sharing and reuse. Today, NWB adoption is substantial: over 500 public NWB datasets totaling over 500 TB across 200,000+ files from 150 worldwide labs are available on the DANDI data archive. NWB's scientific impact is demonstrated by over 180 publications reusing this data and over 2 PB of global downloads. Furthermore, the ecosystem is supported by a mature core software stack with APIs in Python, Matlab, and C++ (PyNWB, MatNWB, AqNWB), advanced tools for data conversion (NeuoConv, NWB GUIDE) and validation tools (NWB Inspector). Over 40 community tools already support NWB.

With the rapid evolution of data acquisition technologies, growing complexity of multi-modal experimental designs, and advances in AI and computing technologies, the NWB data standard must be able to adapt. To ensure long-term reliability, NWB is formally governed by an Executive Board and a Technical Advisory Board. Central to NWB's community-governance model is the NWB Enhancement Proposal (NWBEP) process. The NWBEP framework provides an open, community-driven mechanism for developing, reviewing, and integrating new features into the NWB standard. Through community Working Groups, the NWBEP framework empowers the community to collaboratively shape the future of neurophysiology data sharing. This poster reviews the current status of NWB and highlights recent and proposed enhancements driven by the NWBEP process and the broader community. We detail the integration of new data modalities, integrations with emerging technologies, and efforts towards cross-standard harmonization. NWBEP001 introduces dedicated data types for storing event data. NWBEP004 adds support for metadata about optical physiology devices and restructures optical physiology data around a general MicroscopySeries data type.

Ultimately, the NWBEP framework ensures that NWB remains a stable, extensible, and production-ready standard. By building better data standards together, the neuroscience community is breaking down data silos, streamlining workflows, and generating FAIR datasets to advance our understanding of the brain.

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Poster

PSTR383: Data Analysis: Software Tools I

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Program #/Poster #: PSTR383.08/LL75

Topic: J.07. Data Analysis and Statistics

Support: R24DA064430
U24MH136628

Title: EMBER-Hearth: NIH BRAIN's Computational Hub for Brain-Behavior Data Exploration, Processing, and Analysis

Authors: *R. HINGORANI[1], N. THOMAS[1], C. BAKER[2], E. C. JOHNSON[1], L. DIAZ[1], R. T. HIDER, Jr.[1], N. E. TREGONING[1], G. BEZOLD[1], N. GUITTARI[1], M. OGG[1], J. B. BOCCANFUSO[4], D. DE FREITAS[4], E. MOYO[4], M. SEEBER[6], M. VALLEJO[6], O. METENKO[7], D. DUNCAN[4], S. S. GHOSH[8], Y. O. HALCHENKO[3], T. D. PEREIRA[9], B. PESARAN[5], N. A. SUTHANA[6], J. B. WAGENAAR[4], H. YI[1], B. A. WESTER[1];
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Abstract: Recent advances in sensing technologies and artificial intelligence continue to drive development of powerful techniques for quantifying organismal behavior (e.g., pose estimation; behavioral segmentation; speech analysis). In parallel, pioneering research programs such as NIH BRAIN's Brain Behavior Quantification and Synchronization (BBQS) program are generating neurobehavioral datasets from numerous species collected in naturalistic environments at unprecedented scales, which will be stored within the program's data archive, the Ecosystem for Multimodal Brain-Behavior Experimentation and Research (EMBER). Realizing the scientific value of these data requires infrastructure that supports scalable, reproducible deployment of analytical tools across shared datasets. To address this need, we present EMBER-Hearth, a computational sandbox to connect data on EMBER to analysis tools

and cloud computing resources to promote collaborative, accelerated, and reproducible science. We highlight two EMBER-Hearth milestones: (1) a cloud-based workflow for training and deploying Social LEAP Estimates Animal Poses (SLEAP), an open-source framework for multi-animal pose tracking (Pereira et al., 2022), on EMBER-hosted datasets; and (2) an example of analysis reproducibility from a standardized EMBER dataset. A key enabler of the first milestone is integration of EMBER with the Pennsieve platform (Goldblum et al., 2025), a cloud-based backend which provides scalable execution of containerized analysis workflows. The implemented analysis workflow retrieves video data and keypoint annotations from EMBER, executes SLEAP training and inference through Pennsieve-managed Amazon Web Services (AWS) resources, and automatically uploads outputs back to EMBER, linking data storage, analysis, and dissemination within a unified ecosystem. The second milestone demonstrates a process for standardizing data from an originally lab-specific format to the community-standard Neurodata Without Borders (NWB), then reproducing published analyses (Seeber et al., 2025) from the standardized dataset. This workflow streamlines reproducibility of published results and provides a foundation for secondary analyses, method development, and cross-dataset comparisons. Together, these efforts establish a functional prototype of a cloud-based brain-behavior data ecosystem integrating standardized datasets, community tools, and scalable computing resources. Future work will support additional analytical tools and compute backends, advancing EMBER-Hearth toward a community resource for collaborative and reproducible neuroscience research.

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Poster

PSTR383: Data Analysis: Software Tools I

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR383.09/LL76

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant U24NS134536

Title: Repository-anchored large language model agents for auditable re-analysis of public neuroscience datasets

Authors: *V. Q. TRUONG, D. DE FREITAS, A. SWITEK, J. FROMMEYER, M. GE, E. T. MOYO, Y. HU, J. B. BOCCANFUSO, J. B. WAGENAAR;
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Abstract: Public neuroscience repositories contain large, curated datasets that could support replication, cross-cohort validation, and methodological follow-up, but most deposits are rarely reanalyzed because credible reuse requires substantial domain expertise and labor. We developed Pennsieve AI Co-Scientist, a deposit-anchored agentic workflow that starts from a public dataset identifier and produces auditable derivative analyses. Given a deposit from Pennsieve, DANDI, or OpenNeuro, Pennsieve AI Co-Scientist inspects repository files and metadata, retrieves linked literature, generates falsifiable hypotheses, executes notebooks against live data, critiques statistical and methodological choices, and writes candidate reports in which each concrete claim is traced to either an executed notebook cell or a resolved bibliographic record.We evaluated Pennsieve AI Co-Scientist on three public deposits spanning cancer immunology and human epilepsy electrophysiology, with emphasis on neuroscience use cases. In a Pennsieve dorsal-root-ganglion electrophysiology deposit, the system initially found a highly significant channel-level interaction between dorsal-root-ganglion level and array type ($p < 0.0001$), but an automated robustness check identified that the combined analysis contained only three animals, with the epineural arm represented by one subject. A subject-level permutation test returned $p = 1.0$, leading the workflow to withhold a manuscript rather than report an unsupported finding. In an OpenNeuro multicenter intracranial electroencephalography/electrocorticography epilepsy deposit, Pennsieve AI Co-Scientist performed a power-extended replication by pooling ds003029 with the HUP iEEG Epilepsy Dataset (ds004100). The pooled neural-fragility model achieved area under the receiver operating characteristic curve (AUC) = 0.68, with a 95% confidence interval of 0.55-0.81, spanning both chance and the preregistered 0.70 evidence threshold. The workflow therefore produced an audited honest-negative report rather than a positive biomarker claim. Across runs, the same AI agent architecture produced three desirable outcomes: a valid synthesis, refusal to publish when subject-level evidence was inadequate, and a caveated negative replication. These results suggest that repository-anchored LLM agents may be most useful not as autonomous discovery engines, but as low-cost, auditable systems for surfacing replications, limitations, and negative results from public neuroscience data.

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Poster

PSTR383: Data Analysis: Software Tools I

Location: WCC Halls A-C

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Topic: J.07. Data Analysis and Statistics

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Title: AI surfaced units in the mouse brain that encode rule updates, task context, and reward vs error outcomes

Authors: *P. RAJESWARAN[1,2], B. HARDCASTLE[2], K. SVOBODA[2], S. R. OLSEN[2], P. CLARK[1];
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Abstract: Large-scale neural recordings contain more structure than manual hypothesis-driven analysis can explore, given the vast space of possible neural encodings, region combinations, and task-relevant epochs. Agentic AI workflows can address this bottleneck by reading neural data, generating hypotheses, and executing analyses at a substantially larger scale. We applied AutoDiscovery (Agarwal et al. NeurIPS 2025) to a large-scale neural dataset. Neuropixels recordings were made in mice trained to make perceptual decisions based on visual or auditory stimuli (the rewarded modality alternated in blocks, cued with 5 instruction trials). We steered the AutoDiscovery agent to explore neural coding for context learning, maintenance, and dynamic routing across the frontal cortex (ACA, PL, ILA, MOs), hippocampus (CA1), and striatum (CP) in a 5-subject pilot. Rather than testing one specified hypothesis, the agent autonomously generated a large hypothesis space, executed analyses, and surfaced prioritized results with reproducible code for expert review. We report three candidate findings from this agentic workflow. First, the agent identified a sparse mPFC and MOs subpopulation (210 units, ~4.4%) with elevated instruction trials firing (per-unit Mann-Whitney U), offering a single unit correlate of previously observed ensemble-level mPFC dynamics during flexible behavior (Karlsson et al. Science 2012). Second, the agent proposed that hippocampal (CA1) and prefrontal (ACA, PL, ILA) units hold the rule via sustained block-dependent shifts in pre-stimulus baseline firing, and found such shifts in 34-54% of units per session (Mann-Whitney U with FDR). These baseline shifts are consistent with independent hypothesis-driven analyses, and complement previous literature on stimulus-evoked PFC rule encoding (Wallis et al. Nature 2001; Reinert et al. Nature 2021). Third, the agent partitioned striatal (CP) units into reward-dependent, error-dependent, and motor-coding subpopulations based on post-lick responses on Hits vs. False Alarms (30.1%, 19.9%, and 50% respectively; Welch's t-test $p<0.05$), recovering known reward and motor coding categories (Schultz et al. Science 1997, Peters et al. Nature 2021) while flagging an error-dependent neural population. These results localize rule updates, contextual maintenance, and reward/error coding to distinct neuronal populations. More broadly, this pilot demonstrates that human-steered agentic AI can uncover interpretable neural coding patterns across a large combinatorial hypothesis space.

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Poster

PSTR383: Data Analysis: Software Tools I

Location: WCC Halls A-C

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Program #/Poster #: PSTR383.11/LL78

Topic: J.07. Data Analysis and Statistics

Title: An Autonomous AI Agent for End-to-End Analysis of Neural Recordings: Decoding Alzheimer's, Parkinson's, and Working Memory from EEG and Spike Data

Authors: ***W. LIU**[1], S. PU[2], J. MA[1];
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Abstract: Rapid advances in machine learning offer unprecedented opportunities for neural data analysis, yet adoption is hindered by the gap between specialized AI methods and the expertise of practicing neuroscientists. Pre-trained models for neural recordings have proliferated across modalities including EEG and extracellular spikes, but their heterogeneous architectures and input requirements make systematic comparison and deployment laborious for non-expert users.We present an autonomous AI agent that supports end-to-end neural data analysis. Given only raw recordings and a natural-language task description, the system: (1) analyzes dataset characteristics and selects appropriate evaluation metrics; (2) constructs a prioritized queue of nine pre-trained models spanning EEG (LaBraM, REVE, CBraMod, EEGPT, EEGMamba, BrainOmni) and spike data (NDT3, MtM, POYO-1); (3) generates and executes preprocessing and model-invocation code in a sandboxed environment; (4) diagnoses suboptimal results and adaptively chooses between local code patching and full strategy replanning; and (5) synthesizes findings into an interpretable report.We evaluated the system on three publicly available benchmarks: 3-class EEG classification of Alzheimer's disease, frontotemporal dementia, and healthy controls (OpenNeuro ds004504, n=88); binary EEG classification of Parkinson's disease vs. controls (OpenNeuro ds004584, n=149); and binary decoding of working memory states from extracellular spike recordings (DANDI 000006). Across 8 independent trials per task, the agent consistently outperformed strong baselines, achieving improvements of +6.1 pp in Macro F1 (AD), +5.8 pp in Balanced Accuracy (PD), and +8.0 pp in Balanced Accuracy (working memory) over the strongest single-model comparison.These results demonstrate that an autonomous AI agent can lower the barrier to applying state-of-the-art neural models, enabling neuroscientists without deep machine learning expertise to leverage cutting-edge methods for clinical and cognitive analyses.

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Poster

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Topic: J.07. Data Analysis and Statistics

Support: NIH Grant U24NS120057
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Foresight workshop prize

Title: Quantifying secondary data reuse across open neuroscience archives

Authors: *B. DICHTER[1], P. ADKISSON[1], R. LY[2], P. J. MINEAULT[3], N. ROSE[4], Y. O. HALCHENKO[5];
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Abstract: Public data archives are now central to neuroscience, yet the scientific return on these repositories, including how often deposited datasets are actually reused in new work, remains poorly quantified. We built an automated pipeline that measures secondary reuse across major archives (DANDI, CRCNS, OpenNeuro) by combining full-text search, citation-graph traversal, and large-language-model classification. One discovery channel tracks direct dataset citations, searching the full-text literature directly for archive and dataset identifiers, extracting dataset IDs via archive-specific patterns and capturing reuse that never cites the original publication. A second channel tracks indirect dataset citations to their primary papers, leveraging repository metadata and DOI extraction, tracing citing papers through the OpenAlex citation graph, and retrieving full text from Europe PMC, PubMed Central, CrossRef, and publisher APIs. Across both channels, every paper is classified as data REUSE, mere MENTION, or NEITHER, and confirmed reuse events are further categorized into eight types (e.g., novel analysis, benchmarking, tool demonstration, model training).
Across archives we identified thousands of reuse events: 300+ papers from DANDI, 390+ from CRCNS (147 datasets spanning 17 years), and 1,500+ from OpenNeuro. Reuse is highly uneven. Mean cumulative reuse per dataset saturates near 3.6 papers for CRCNS, although 53% of CRCNS datasets have never been reused. OpenNeuro instead shows quadratic, non-saturating growth. Cox proportional-hazards (Andersen-Gill) modeling reveals that data tends to be reused more if the corresponding paper has more citations, and that neurophysiology data from primates tends to be reused more than data from other species. We find examples of many different types of reuse, including analysis development and benchmarking, aggregative analysis, confirmatory analysis, training machine learning models, and use in educational materials. Notably, 93% of DANDI reuse papers cite only the primary publication and never the dataset itself, meaning standard data-citation metrics drastically undercount real reuse.
These results provide the first cross-repository, full-text-validated estimates of neuroscience data reuse and identify the factors that drive it, informing archive design, funder data-sharing policy, and credit attribution for data producers.

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Poster

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Program #/Poster #: PSTR383.13/LL80

Topic: J.07. Data Analysis and Statistics

Support: JSPS KAKENHI Grant Number 26K09521

Title: RFind, an interpretable single-cell scoring method for quantifying gene expression states

Authors: *T. MURANO[1], T. MIYAKAWA[2];
[1]Fujita Hlth. Univ., Toyoake, Japan; [2]Fujita Hlth. University, ICMS, Div. Syst. Med., Toyoake, Japan

Abstract: To understand the pathophysiology of psychiatric disorders, it is crucial to capture gene expression changes in the brain. Transcriptomic studies of human postmortem brain tissue have reported alterations in diverse gene groups across various psychiatric disorders (Gandal et al., 2018), and our group has shown that expression changes related to neural hyperactivity and cellular maturity are shared across schizophrenia and other neuropsychiatric disorders (Murano et al., 2019). More recently, single-cell RNA-seq (scRNA-seq) has increasingly revealed the cell types in which disease-related expression changes occur (Ruzicka et al., 2024; Nishioka et al., 2026). Dimensionality reduction methods such as UMAP and t-SNE are widely used to visualize scRNA-seq data; however, dimensional compression reduces the interpretability of the resulting axes, making it difficult to directly interpret what biological states are reflected by the visualized cell populations.
Here, we developed RFind, a novel statistical method designed to expand the interpretability of scRNA-seq data. RFind adapts the Running Fisher method (Kupershmidt et al., 2010), which evaluates similarity between two gene lists, to quantify the similarity between each cell's gene expression pattern and a reference gene list. This enables multidimensional evaluation of cellular expression states using biologically interpretable indices. To validate the utility of RFind, we obtained a publicly available scRNA-seq dataset of hippocampal cells from mice subjected to social stress (De Donno et al., 2026). Using RFind, we calculated each cell's similarity to reference lists related to stress response, neural hyperactivity, and cellular maturation state. The stress response index differed between stress-exposed and control groups, and this change was particularly pronounced in oligodendrocytes. These results indicate that RFind can quantitatively evaluate differences in gene expression states at the single-cell level using interpretable biological indices. Future applications of this method to patient samples and disease model animals may help quantify disease-related gene expression patterns at the single-cell level and provide a basis for understanding the molecular pathophysiology of psychiatric disorders.

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Poster

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Topic: J.07. Data Analysis and Statistics

Support: The BRAIN Foundation
Ara Parseghian Medical Research Fund

Title: NEURAL: Novel High-Throughput Method for Automated Detection of Synaptic Activity via Live Imaging for in Vitro Neuronal Cultures

Authors: *C. D. SANDER[1,2], S. FRYE[1], Y. CHEN[1], J. HARTWEGER[1], G. OATMAN[1], J. BERGQVIST-PATZKE[1], A. WENNINGER[1], P. FLYNN[3], C. PATZKE[1];
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Abstract: To understand how genetic mutations and physiological conditions affect synaptic activity in neurons, fluorescent sensors have been engineered to detect calcium and neurotransmitters such as glutamate and GABA. Sensors like GCaMP, iGluSnFR, and iGABASnFR can be robustly and rapidly expressed in target cells via the lentiviral system. Recordings of changes in fluorescence are then used as a proxy for neurotransmitter release and network activity. While computational pipelines exist for analysis of in vivo live imaging data, few tools exist for analysis of in vitro live imaging, so labor-intensive and subjective analysis processes are commonly used. To address these concerns, we developed a novel computational system, NEURAL: Network-based Extraction with Unbiased ROI Analysis in Live-imaging. NEURAL utilizes custom-trained convolutional neural networks to identify ROIs (regions of interest) in in vitro live imaging videos, outperforming alternative automated approaches for ROI detection. This work provides both neural network models trained on a wide range of live imaging data and simple infrastructure for researchers to train custom neural networks specific to their needs.
NEURAL is validated via six experiments with a range of setups: either primary mouse culture or stem-cell derived human neurons undergo calcium, iGluSnFR, or iGABASnFRn imaging, with imaging buffers of differing ion concentrations or acute delta-9-tetrahydrocannabinol (THC) applications. We find that NEURAL recovers expected biological outcomes, with comparable or improved sensitivity relative to manual alternatives. While we identify PeakCaller as an effective peak detection algorithm for positive-going sensors (calcium imaging, iGluSnFR), we develop a novel approach for analyzing negative-going sensors (iGABASnFRn). Additionally, NEURAL provides new metrics for analyzing bursts of activity, widening the range of biological questions that can be answered regarding synaptic transmission in in vitro models. Ultimately, NEURAL minimizes labor and bias while enabling reliable analysis of synaptic events from live imaging data. Our versatile approach makes NEURAL applicable for a wide range of experimental designs, and capable of performing analysis on novel fluorescent sensors.

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Poster

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Topic: J.07. Data Analysis and Statistics

Support: NIH 2R44 MH125238

Title: Interactive Block-Wise Python Scripting in syGlass VR

Authors: M. MOREHEAD[1], N. SPENCER[1], *G. A. SPIROU[2];
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Abstract: Introduction: High-resolution and large-volume 3D, such as those generated by light-sheet or electron microscopy, present immense challenges for both visualization and analysis due to their terabyte-scale size. Virtual Reality (VR) platforms like syGlass have revolutionized the exploration of these massive datasets using hierarchical image pyramids. However, a persistent bottleneck remains: seamlessly bridging the gap between immersive, user-guided visualization and automated, custom image-processing pipelines.
Methods: To address this, we developed a novel, custom Python script system integrated directly into the syGlass hierarchical image pyramid ecosystem. Leveraging the chunked, multi-scale OME-Zarr data format, this system empowers users to deploy custom Python scripts against specific 3D volumes or sub-volumes. Utilizing VR controllers, researchers can intuitively select regions of interest (ROIs) within the immersive environment. The system dynamically extracts the corresponding OME-Zarr data blocks, feeds them into the local Python environment, and executes the pipeline block-wise, minimizing memory overhead while maximizing processing efficiency.
Results: As a primary application of this ecosystem, we present Hypertrace, a new automated axon and blood vessel tracer. Hypertrace is deployed block-wise directly within user-selected sub-volumes. By combining intuitive spatial targeting via VR with advanced Python-based tracing algorithms, Hypertrace allows researchers to instantly isolate complex vascular and neural networks, trigger automated local segmentation, and immediately visualize the rendered 3D tracing results in real time.
Conclusion: This integration of interactive VR selection, standardized OME-Zarr data structures, and arbitrary Python execution provides a highly scalable, extensible framework for large-scale neuroscience data analysis. It successfully unites human spatial intuition in VR with the power of automated programmatic segmentation.

Disclosures: M. Morehead: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); syGlass, Inc. **N. Spencer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); syGlass, Inc. **G.A. Spirou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); syGlass, Inc.

Poster

PSTR383: Data Analysis: Software Tools I

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Support: This research was supported by the Commercialization Promotion Agency for R&D Outcomes(COMPA) funded by the Ministry of Science and ICT(MSIT).(2710093464)

Title: Deep Learning-Based 3D Pose Tracking for Itch-Related Behavioral Phenotyping in Atopic Dermatitis

Authors: *S. PARK[1], E. KIM[2], H. CHA[3], K.-T. KIM[4], B.-H. KIM[5];
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Abstract: Itch is one of the most debilitating symptoms of atopic dermatitis, yet it remains difficult to quantify objectively in clinical and preclinical studies. NC/Nga mice are a well-established model of atopic dermatitis-like itch because they exhibit spontaneous scratching that reflects disease severity and contributes to dermatitis progression. However, scratching and grooming in this model are still usually evaluated by manual observation or device-specific systems, which limits throughput, reproducibility, and standardization.To address this gap, we developed a deep learning-based pipeline combining markerless 3D pose tracking with behavioral classification to objectively phenotype itch-related scratching and grooming in DNCB-induced NC/Nga mice. Eleven-week-old NC/Nga mice were used as an atopic dermatitis model. On day 0, the upper back and both auricles were shaved, and residual hair was removed to expose the dorsal skin and ears. 1% DNCB and 0.2% DNCB were then applied to induce atopic dermatitis-like lesions and spontaneous scratching. Behavioral videos of freely moving mice were acquired using a synchronized five-channel multi-camera system.Markerless 2D keypoints were detected in each view using a DeepLabCut v2.3.11-based network trained to identify user-defined anatomical landmarks, including the nose, ears, forepaws, hindpaws, tail base, and trunk points. Camera calibration and multi-view triangulation were then used to reconstruct 3D body trajectories, enabling quantitative analysis of scratching and grooming kinematics. To improve model quality, approximately 50 to 100 frames were selected across five views using DeepLabCut k-means-based frame extraction, capturing diverse postures under different viewing angles and illumination conditions. Keypoints were annotated using consistent anatomical definitions, and low-confidence or high-error predictions were iteratively refined through an active-learning loop.The resulting sequential 3D keypoint trajectories were normalized and used as input to a deep learning-based temporal classifier to distinguish scratching, grooming, and other behaviors. This framework provides an objective and scalable platform for itch-related behavioral phenotyping in DNCB-induced NC/Nga mice. Compared with conventional 2D or manual approaches, it is expected to improve discrimination between

scratching and grooming-like movements, supporting more standardized behavioral endpoints for atopic dermatitis research and preclinical therapeutic evaluation.

Disclosures: S. Park: A. Employment/Salary (full or part-time):; PLASBIO Inc. **E. Kim:** A. Employment/Salary (full or part-time):; PLASBIO Inc. **H. cha:** A. Employment/Salary (full or part-time):; PLASBIO Inc.. **K. Kim:** None. **B. Kim:** None.

Poster

PSTR383: Data Analysis: Software Tools I

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Program #/Poster #: PSTR383.17/LL84

Topic: J.07. Data Analysis and Statistics

Title: Development and Validation of a Cartesian Stereotaxic Device for Precise Neurosurgical Procedures in Rodent Models

Authors: *C. JIMÉNEZ-ROMÁN[1], R. BELTRAN-RAMIREZ[2], J. MARTINEZ-MENDOZA[3], X. M. BECERRA-GONZÁLEZ[4], J. A. DOMINGUEZ-RAMIREZ[5];
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Abstract: Stereotaxic surgery is an essential technique in experimental neuroscience, enabling precise access to specific brain regions for electrode implantation, cannula placement, microinjections, and neurophysiological studies. However, conventional stereotaxic systems are often expensive, difficult to transport, and may present limitations in animal stabilization and positioning accuracy. The objective of this study was to develop and evaluate a novel Cartesian stereotaxic device designed to improve stability, precision, and usability during neurosurgical procedures in rodent models.The device incorporates a Cartesian positioning system with independent X, Y, and Z axes controlled through precision lead screws. The platform includes a modular animal fixation mechanism consisting of a snout holder, bilateral actuators for cranial stabilization, and a stereotaxic arm capable of supporting surgical instruments, electrodes, and cannulas. Additional features include foldable support legs with suction-based fixation to improve stability and facilitate storage and transportation.Prototype validation was conducted using laboratory rodent models under controlled experimental conditions. The stabilization system effectively immobilized the animal's head while allowing precise positioning of surgical instruments. The Cartesian architecture enabled reproducible targeting of predetermined coordinates and facilitated controlled advancement of electrodes and cannulas into selected brain regions. The lead screw mechanisms maintained positional accuracy throughout the procedures, minimizing unintended displacement during manipulation.The device demonstrated reliable performance for stereotaxic interventions commonly employed in neuroscience research. Its modular design, portability, and enhanced fixation capabilities provide a practical alternative to conventional systems while maintaining the precision required for experimental applications.

This technology may support studies involving neural circuit mapping, intracerebral drug delivery, electrophysiological recordings, deep brain targeting, and other preclinical neuroscience investigations. The proposed platform represents an accessible stereotaxic solution that may improve reproducibility and experimental efficiency in neuroscience laboratories.

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Poster

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Program #/Poster #: PSTR383.18/LL85

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant AA030061

Title: Utilizing deep-learning software Social LEAP Estimates Animal Poses (SLEAP) and a lickometer device for tracking mouse home cage ethanol drinking behavior

Authors: *E. K. HOSKINSON[1], H. SIDDIQUI[2], S. E. RODARTE[3], A. M. ACUNA[4], M. OLIVE[5];
[1]Psychology, [2]Arizona State Univ., Phoenix, AZ; [4]Sch. of Life Sci., [5]Psychology, [3]Arizona State Univ., Tempe, AZ

Abstract: Animal models of substance use disorders are useful in understanding reward and motivation toward drugs of abuse. Quantifying microstructural drinking behaviors is important for understanding the features of ethanol consumption in mice, particularly in transgenic mouse models of alcohol use disorders. Here, we describe a methodology for using SLEAP (Social LEAP Estimates Animal Poses) alongside a lickometer to track home-cage binge-like ethanol (EtOH) drinking with high temporal and spatial precision in conjunction with wireless optogenetic neuromodulation. When pairing this deep-learning system with a lickometer, consumption-related behaviors are analyzed at a microstructural level by tracking licking events, frequency and duration of drinking bouts, and proximity to the drinking spout. Mice are first infused with viral vectors encoding commonly utilized neuromodulatory opsins, and following recovery and implantation of wireless optogenetic receivers, placed in their home-cage with an EtOH solution for 2hr/day/4 days and recorded using a video camera. Bottle weights are taken before and after sessions to calculate the volume of EtOH solution consumed, and each optogenetic stimulation is captured by wireless receiver LEDs. Afterward, video recordings are transferred to SLEAP. Consummatory behaviors are analyzed using a lickometer device, which records interruptions of an infrared beam to document a “licking event”. An Arduino board is programmed with a custom C++ script to track microstructural behaviors, including: number of licks, number of bouts, average bout latency, latency to first lick, and latency to first bout. This combination of SLEAP, wireless optogenetics, and a home-cage lickometer device allows for

convenient cross-referencing of drinking-related behaviors following optogenetic neuromodulation to reveal greater insight into EtOH consummatory behaviors.

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Poster

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Program #/Poster #: PSTR383.19/LL86

Topic: J.07. Data Analysis and Statistics

Title: Scientific Knowledge AI (skai): A Unified Agent-Based Interface for Distributed Scientific Infrastructures

Authors: *A. HEINSFELD, F. PESTILLI;
Dept. of Psychology, The Univ. of Texas at Austin, Austin, TX

Abstract: Modern neuroscience increasingly relies on a rapidly expanding ecosystem of data repositories, computational platforms, and knowledge resources. Initiatives such as the U.S. BRAIN Initiative, DANDI, OpenNeuro, UK Biobank, and brainlife.io have made large-scale neuroimaging, neurophysiology, and molecular datasets broadly accessible. However, effectively using these resources remains challenging. Researchers must navigate diverse interfaces, metadata standards, authentication systems, and computational environments, often translating scientific questions into platform-specific workflows that span multiple systems.We argue that a major limitation of modern neuroscience infrastructure is no longer data availability or computational capacity, but the difficulty of interacting with increasingly distributed scientific resources. Although technical interoperability has improved, researchers still face substantial cognitive and procedural burdens when discovering datasets, integrating information across platforms, and coordinating analyses. As the number of available resources continues to grow, these challenges increasingly constrain scientific productivity and data reuse.To address this problem, we developed Scientific Knowledge AI (skai), an extensible agent-based framework that enables natural-language interaction with heterogeneous scientific infrastructures. skai combines large language model reasoning, semantic validation, and protocol-driven interoperability to translate scientific goals into coordinated workflows spanning data repositories, computational platforms, and knowledge bases. The system operates through infrastructure-defined application programming interfaces (APIs) and standardized interoperability protocols such as Model Context Protocol (MCP), allowing resources to remain distributed while preserving governance, authentication, and access-control policies.By establishing a unified interaction layer between researchers and scientific infrastructures, skai transforms fragmented resources into a coherent environment for data discovery, workflow orchestration, and scientific reasoning. This approach enables neuroscientists to interact with

data, tools, and knowledge using natural language, reducing technical barriers to cross-platform analyses and facilitating integrative discovery across scales, modalities, and domains.

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Poster

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Support: NIH Grant U01NS137250

Title: NEURD 2.0: End-to-End Machine Learning-Based Automated Proofreading and Feature Extraction

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Abstract: In an era in which volumetric electron microscopy (EM) datasets can reach millimeter scale at nanometer resolution (Shapson-Coe et al., 2021; Consortium et al., 2021), automatic segmentations can produce highly detailed 3D reconstructions of individual cells. These reconstructions still contain merge and split errors that require proofreading for rigorous analysis. Existing heuristic and machine learning approaches improve some error types, but no method robustly corrects all errors across datasets. To begin to address this need, we present an extension of NEURD, a heuristic-based error correction package that we have successfully applied to correct a variety of error types in the MICrONS Minnie65 and H01 datasets (Celii et al., 2025). NEURD decomposes neurons into extensively-annotated graphs using manually tuned parameters, and then applies a set of heuristic graph filters to resolve merge errors (achieving synaptic precision scores of > 87% for both axon and dendritic segments on both datasets). *NEURD 2.0* aims to replicate the entire NEURD pipeline in an end-to-end machine learning solution, to learn merge and split error corrections directly from data. Starting from the coarse, feature-rich NEURD graphs, a graph neural network (GNN) trained for binary merge error prediction (N=4814) is able to replicate the results of the original NEURD heuristic model and transfer this performance to different volumes collected with similar methods: MICrONS Minnie35 (precision = 0.95, recall = 0.75, N = 1687) and an independent cortical EM dataset (precision = 0.94, recall = 0.52, N = 27075). When clustering GNN activations for predicted error nodes, the original heuristic error classes can be recovered (GMM with number of clusters = 5, purity = 0.737). Furthermore, several clusters represented high-fidelity error subsets, and we were able to apply nearly 600,000 high-fidelity corrections (human validation at 98% over 300

edit test set) back to the original datasets. In the case of split errors, after using the NEURD decomposition graphs to predict termination points, a simple supervised XGBoost algorithm can then be trained to predict the correct extension from the thousands of possible segments around the termination point with a top-5 accuracy of 0.93. This recall can be increased to a top-1 accuracy of 0.95 (at a recall of 0.17), by applying a threshold on the model's confidence (neurons = 517, true extensions = 453, all extension candidates = 148,082). NEURD 2.0 represents an advance towards a generalizable and comprehensive automated proofreading tool for diverse EM datasets, advancing our ability to query them for scientific insight.

Disclosures: B. Celii: None. **N. Patel:** None. **I. Western:** None. **M. Hu:** None. **D. Xenes:** None. **M. Robinette:** None. **C.A. Bishop:** None. **B.A. Wester:** None. **P.K. Rivlin:** None. **J. Reimer:** None.

Poster

PSTR383: Data Analysis: Software Tools I

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR383.21/LL88

Topic: J.07. Data Analysis and Statistics

Support: VA MERIT I01RX003498
BLR&D: 1I01BX006511
VA SPiRE I21 RX004629-01A1

Title: An integrated pipeline for chronic, synchronized video and high-density electrophysiology in a porcine model of posttraumatic epilepsy

Authors: *M. ROSALINO[1], A. V. ULYANOVA[3], J. A. WOLF[2];
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Abstract: Porcine models in neuroscience represent an emerging model that is highly translational in comparison to traditional rodent models. These models are biomechanically more realistic, and therefore may elucidate mechanisms of Posttraumatic Epilepsy (PTE) following Traumatic Brain Injury (TBI). However, these conditions often progress on an unpredictable scale, often taking months to develop. Monitoring for such conditions is a highly involved process, one in which cutting edge video and electrophysiological monitoring is essential.
The nature of PTE mandates continuous monitoring, including the usage of cameras allowing for 24/7 coverage. Metrics such as velocity, distance covered in a day, sleep cycles, and behavioral seizure correlates can all be monitored using features extracted from this video record. Similarly, advanced wireless electrophysiology can be utilized to enhance our understanding of PTE with near continuous monitoring of a wide variety of brain regions including the cortex and hippocampus. We have therefore implemented up to 256 channel recordings of 30kHz sampled data from these animals. Correlations between this electrophysiological data and associated

clinical features are therefore the gold standard for evaluating PTE in these models.
We will therefore present an integrated pipeline of analysis that has been utilized to track chronic post sham and TBI animals for periods of up to one year post implantation. We have developed machine-learning based algorithms to detect pig location and movement transitions, all of which can be run at at a fraction of real-time. In addition, methodology for synchronization of the high-density electrophysiology with video frames for correlational analysis has been implemented, allowing for chronic analysis of oscillatory activity and changes post-injury that correlate with movement. These metrics have been utilized to analyze home-cage location, activity, sleep-stages, and even behavioral interactions with cage adjacent pigs, allowing for a rich analysis of TBI vs. non-TBI pigs.
In addition, continuous video as well as high density/richly sampled electrophysiology presents a number of challenges for storage and analysis of large datasets. We will therefore present solutions for these technical and analytic challenges for large datasets that can be applied to chronic recordings across species and disease models.

Disclosures: M. Rosalino: None. **A.V. Ulyanova:** None. **J.A. Wolf:** None.

Poster

PSTR383: Data Analysis: Software Tools I

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR383.22/LL89

Topic: J.07. Data Analysis and Statistics

Support: DoD Vannevar Bush Faculty Fellowship
Howard Hughes Medical Institute

Title: NeuroAI-Bench and NeuroAI-Agent: a framework for autonomous neuroscience analysis and exploration

Authors: *Y. JIANG[1,2,9,10,12], R. T. CHRAPKIEWICZ[1,9,12], C. SYLBER[3,9], K. SHENG[4], Y. GAO[13], A. SRINIVASAN[3,10], T. H. KIM[14,12], O. JAIDAR[1,12], M. BLANCO-POZO[1,9,12], Y. SHIKANO[1,12], H. LIM[1,10], X. JIANG[1,10], L. WANG[1,10], X. SUN[1,11], Y. JIANG[15], J. LUO[14,12], C. HUANG[16], I. D. LANDAU[5], O. HAZON[6,9,10], Y. LI[7,10], G. CHATTREE[1,10], Y. B. WENG[6,9,10], M. J. REDINBAUGH[1,10], S. LINDERMAN[8,17], M. J. SCHNITZER[18,10,9,12,17];
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Abstract: AI coding agents are entering scientific work yet have mainly been designed and tested for software-engineering tasks. Whether coding agents can reliably analyze and explore complex neuroscience datasets and return trustworthy results is an open question. Rigorous analysis takes more than running code; scientific exploration proceeds through many iterations and field-specific workflows, and interpreting each result properly requires knowledge of the underlying biology, not just skill in data analytics.
To enable autonomous analyses in neuroscience, we first built NeuroAI-Bench, the first benchmark of its kind in the field, which we assembled from published and unpublished datasets and accompanying analyses vetted by human domain experts. It comprises >30 tasks across >15 datasets and >500,000 neurons spanning different species and recording modalities, covering data quality control, inferential analysis, method selection, hypothesis testing, and audit of flawed analyses. Each task specifies a scientific question, the dataset to be used, and the required deliverables, allowing agents to infer suitable methods, controls, and interpretations. Grading of agent performance combines deterministic checks on the outputs with expert rubrics that assess scientific reasoning. In tests of whether off-the-shelf coding tools such as Claude Code and Codex could solve these tasks, we found that they struggled to follow the scientific intent, were harder to steer even with customization efforts, and, when they did produce an answer, left fewer traces of how the results were achieved.
We then built NeuroAI-Agent, an open framework whose execution is restricted to pre-approved analysis tools and workflows that are already accepted in the field. It runs several workflows that are performed by digitized personas from a neuroscience lab. We used different AI agents that respectively play a neuroscientist, a data scientist, a librarian that searches the published literature through vector embeddings, a data engineer that prepares and checks the data, and analysts, statisticians, and reviewers. These personas are stacked to mimic how neuroscientists typically work, down to formulating results and reaching conclusions, and the workflows include predefined cross-specialty iteration loops, such as a neuroscientist agent evaluating a statistician agent's output. Every result carries a full audit trail of how it was produced. On NeuroAI-Bench, this system outperformed off-the-shelf coding tools while adding complete traceability. We intend this work to seed further development toward autonomous, trustworthy, and fully traceable neuroscience analysis at scale.

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Poster

PSTR383: Data Analysis: Software Tools I

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Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR383.23/LL90

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant R01DC019639

Title: Evaluating LeCoder as an Automated Coding Tool for the Philadelphia Naming Test in Post-Stroke Aphasia Research

Authors: *A. MCMAHON[1], M. SYDNOR[2], M. A. JOHNSON[2], B. LAMMERS[2], J. L. MURTER[2], R. SEBASTIAN[2];
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Abstract: Aphasia is a devastating consequence of stroke that significantly impairs naming ability. Naming is commonly assessed with confrontation tests such as the Philadelphia Naming Test (PNT), which scores patient responses as either accurate or inaccurate. Naming error analysis can provide additional insight into the linguistic mechanisms underlying aphasia recovery. On the PNT, errors are classified into seven categories: correct (R), semantic (S), phonological (F), nonword phonological (N), unrelated (U), nonword unrelated (NU), and mixed (M) error. Manual error coding is labor-intensive and prone to inter-rater variability, as the subjective nature of semantic and phonological similarity judgments can produce inconsistent classifications across coders and research groups. LeCoder is an open-source automated tool designed to address these limitations by objectively classifying target-response pairs into the seven PNT error categories. We examined the accuracy, consistency, and error patterns of LeCoder applied to pre-treatment PNT responses from 20 participants enrolled in our ongoing clinical trial on cerebellar stimulation in aphasia rehabilitation (NCT05093673). Manual coding was performed by trained researchers, and inter-rater reliability was established via Speech-Language Pathologist review of 25% of entries. Analyses included Wilcoxon signed-rank t-tests and non-parametric correlations. LeCoder achieved a median agreement of 91.7% (IQR: 84.9-93.2%; κ=0.80), with broad correct/incorrect accuracy reaching a median of 100.0%, indicating most disagreements reflected error subtype rather than correct/incorrect classification. Significant directional biases were identified for all six code types (BH-corrected Wilcoxon, all $p<0.05$). Semantic errors were most underrepresented (−5.13%, $p<0.0001$), which seems to have been driven by phonological over-sensitivity and by polysemy. Phonological real-word errors were overrepresented (+3.18%, $p<0.0001$), potentially largely attributable to rare-word miscoding. Overall accuracy correlated significantly with aphasia severity. These findings support LeCoder as a promising tool for large-scale aphasia research, particularly for participants with lower aphasia severity, while identifying real-word sensitivity and polysemy handling as key targets for refinement.

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Poster

PSTR383: Data Analysis: Software Tools I

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Program #/Poster #: PSTR383.24/LL91

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant DA062121

Title: I-ROCKET: An Interpretable Time-Series Classifier for Neural Signal Analysis

Authors: *M. LAUBACH;
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Abstract: Time-series classification (TSC) methods offer a powerful alternative to hypothesis-driven analyses of neural signals. Standard approaches to applying classifiers from machine learning, such as SVMs and Random Forest, as commonly applied require prior assumptions about relevant frequency bands and time windows. By contrast, TSC methods learn discriminative features directly from the data. We developed I-ROCKET, an interpretable extension of the MultiRocket classifier (Tan et al., 2022), and applied it to local field potential (LFP) recordings from rat prefrontal cortex. The package is available on GitHub: https://github.com/LaubachLab/I-ROCKET. MultiRocket transforms time series into feature vectors using random convolutional kernels and pooling operators. Our I-ROCKET extension adds to this framework in three ways. First, it exposes all kernel properties, enabling inspection of the features driving classification. Second, it implements feature selection using shrinkage-t scoring (Opgen-Rhein and Strimmer, 2007) and stability analysis (Meinshausen & Bühlmann, 2010; Nogueira et al., 2018). Third, it provides graphical methods to visualize the kernel patterns and activations and, most importantly, to generate composite kernel activations for each trial in a dataset. Together, these extensions allow the classifier to extract discriminative signals that can be analyzed with standard spectral and time-frequency methods. We applied I-ROCKET to LFP recordings from rat prefrontal cortex during a reward context task (Amarante et al., 2017; Amarante and Laubach, 2021). Discriminative kernels identified signals with phase-amplitude coupling between delta phase and beta and gamma amplitudes. These coupled signals tracked reward context. They were not obvious from spectral analyses of the raw LFP. Our findings show that I-ROCKET can recover interpretable neural dynamics without prior specification of frequency bands or time windows.

Disclosures: M. Laubach: None.

Poster

PSTR383: Data Analysis: Software Tools I

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Program #/Poster #: PSTR383.25/LL92

Topic: J.07. Data Analysis and Statistics

Support: NIA Grant 1R44AG090130-01A1

Title: Brain-Wide Parenchymal Measurement of BBB-Crossing Human IgG-Based Antibody Therapeutics

Authors: J. ZEITOUN[1], A. REKSOATMODJO[1], ***C. REDD**[1], B. PEKAREK[2,1], S. P. GANDHI[3], D. G. WHEELER[1,4], P. CHEUNG[1];
[1]Translucence Biosystems, Irvine, CA; [2]Res., Pekarek Lab., Berkeley, CA; [3]Neurobio. and Behavior, Univ. of California, Irvine, CA; [4]Activity Signaling, LLC, San Diego, CA

Abstract: Despite major advances in tissue labeling and imaging technologies, imaging more than a few hundred microns into tissue has historically required sectioning and mounting thin tissue slices on glass slides. When studying genetic or pharmacological manipulations that may affect the entire brain, this region-focused approach can limit discovery by restricting analysis to predefined areas of interest. Tissue clearing combined with light-sheet microscopy overcomes these limitations by enabling intact-brain imaging and providing comprehensive, unbiased anatomical and functional insights at the whole-organ level. We have applied these methods to quantify the brain-wide distribution of next-generation antibody therapeutics that use receptor-mediated transport mechanisms to shuttle antibodies across the blood-brain barrier (BBB). A key challenge in evaluating BBB penetration is that BBB-crossing antibodies can remain highly enriched within vascular endothelial cells, making it difficult to distinguish true therapeutic delivery to the brain parenchyma, where most drug targets reside. Here, we demonstrate the fine-tuning of the convolutional neural network (CNN) tUbeNet using a minimal training and validation dataset to segment human IgG-positive blood vessels and isolate the parenchymal compartment in whole-brain light-sheet microscopy datasets. The resulting model was validated across six independent whole-brain datasets containing blood vessel-specific fluorescence labeling. Segmented vasculature from randomly selected image crops was compared with hand-annotated ground truth to assess model performance, including precision, accuracy, false-positive rates, and false-negative rates. Our results indicate that fine-tuning tUbeNet on a light-sheet-specific dataset enabled robust and generalized recognition of vascular morphology in volumetric light-sheet images. This finding is notable because the original model was not trained on large light-sheet datasets, further supporting tUbeNet's ability to generalize vascular features across microscopy modalities. These specialized yet computationally efficient models can support large-scale studies of BBB-penetrant antibody therapeutics for Alzheimer's disease and other neurological disorders, as well as complementary therapeutic approaches such as focused ultrasound, where accurate quantification of BBB transit is essential.

Disclosures: J. Zeitoun: None. **A. Reksoatmodjo:** None. **C. Redd:** None. **B. Pekarek:** None. **S.P. Gandhi:** None. **D.G. Wheeler:** None. **P. Cheung:** None.

Poster

PSTR383: Data Analysis: Software Tools I

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR383.26/LL93

Topic: J.07. Data Analysis and Statistics

Title: A Novel Semi-Automated Workflow for 2D Glial Morphological Analysis: Implications for COPD

Authors: ***G. L. BLISSETT**[1], J. A. SEYSENER[1], P. JOBLING[1], J. C. HORVAT[1,2], K. F. BUDDEN[2,1], M. A. TADROS[1];
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Abstract: Glial morphology is a well-characterised indicator of neuroinflammation. Existing quantitative methods have been developed predominantly for 3D confocal z-stack data, however 2D immunofluorescent preparations remain standard in preclinical research, and robust pipelines for 2D glial morphology analysis remain underdeveloped.
CellSelect-3DMorph (York et al., 2018; Taborda-Bejarano et al., 2025) provided the developmental framework for 2DMorph. Its volumetric operations were systematically deconstructed and redeveloped for 2D single-plane imaging, prioritising segmentation accuracy, reproducibility, and user accessibility. The resulting pipeline differs substantially from its predecessor in segmentation logic, quantitative scope, and user interaction, resolving touching cells via skeleton-topology splitting, detecting soma through iterative skeletal pruning, and extracting 38 morphological parameters. Male C57BL/6 mice received daily intranasal CSE (100%) or saline for two weeks (ethics: A-2023-312). 20µm coronal sections were immunolabelled for IBA1 (microglia) and GFAP (astrocytes) and imaged from the DG by epifluorescence microscopy (Olympus BX51/DP72; cellSens; 10×; 5760 × 3600 pixels). Validation was performed against manually binarised ground truth masks (n = 28/cell type) using precision, recall, Rand index, Dice coefficient, and Jaccard index.
2DMorph demonstrated strong segmentation performance for microglia (precision 0.959 ± 0.027, recall 0.968 ± 0.022, Dice 0.963 ± 0.009, Jaccard 0.929 ± 0.016) and astrocytes (precision 0.978 ± 0.019, recall 0.925 ± 0.029, Dice 0.950 ± 0.010, Jaccard 0.906 ± 0.018). Preliminary findings (n = 4/group) indicate unchanged microglial density following CSE, with reductions observed in microglial cell area and ramification index. Concurrent reductions in astrocyte cell density, cell area, and ramification index were also observed. Data collection is ongoing.
2DMorph addresses a critical methodological gap in preclinical neuroinflammation research, demonstrated by its detection of preliminary glial morphological alterations in the DG of a CSE model of COPD. Its open-source MATLAB architecture suggests broad applicability across imaging modalities and disease models, warranting further validation.

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Poster

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Program #/Poster #: PSTR383.27/LL94

Topic: J.07. Data Analysis and Statistics

Support: NIH R24-MH-114793
NIH R50-MH-141899

Title: The Brain Image Library: Designing Features for Spatial Transcriptomics Discovery, Search, and Visualization

Authors: *A. J. ROPELEWSKI[1], **M. KENNEY**[2], L. TUITE[2], I. CAO-BERG[2], E. SMITH[4], B. BINTU[4], A. M. WATSON[6], K. KEDZIORA[3], I. JENIE[4], D. BORDELON[2], E. MISHKIN[5]; [1]Carnegie Mellon Univ., Moon Township, PA; [3]Pittsburgh Supercomputing Ctr., [2]Carnegie Mellon Univ., Pittsburgh, PA; [4]UC San Diego, San Diego, CA; [5]UC San Diego, Lafayette, CA; [6]Univ. of Pittsburgh, Bethel Park, PA

Abstract: The rapid evolution of spatial transcriptomics technologies has revolutionized our understanding of structural and cellular heterogeneity. However, the scale and complexity of these datasets present significant challenges for standardization and long-term preservation. The Brain Image Library (BIL), funded by the National Institutes of Health, serves as a specialized repository for light microscopy data. Historically, BIL has served as a repository for 3D whole-brain microscopy. Here, we present new infrastructure and specializations developed to establish BIL as a primary repository for imaging-based spatial omics data.

To address the unique demands of spatial biology, BIL has implemented new features within its established ecosystem. First, we developed a robust metadata schema to ensure that essential experimental parameters, including tissue registration and probe/gene panels, are captured to enhance data reproducibility and reusability. Second, we developed a cross-dataset, single-cell gene search utility. Because finding specific biological features across multiple large-scale datasets can be a barrier, this search feature is optimized for spatial data matrices. Users can query specific genes across hundreds of datasets simultaneously to identify, filter, and access relevant data. Lastly, BIL adapted MERFISHEYES to provide instant web-based visualization for large-scale spatial data. This tool allows users to navigate and compare multi-terabyte datasets and overlay gene expression data to inspect cellular architecture directly within a web browser.

Collectively, these enhancements streamline access for spatial transcriptomic analysis and discovery. By lowering computational barriers, we aim to empower the global neuroscience community to fully utilize and analyze these large-scale datasets.

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Poster

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Location: WCC Halls A-C

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Program #/Poster #: PSTR383.28/LL95

Topic: J.07. Data Analysis and Statistics

Title: A novel automated assay for quantifying lateral motor behavior in preclinical stroke models

Authors: L. MESSE, *S. SANTOS, S. REYES-ESTEVES;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Hemorrhagic and ischemic strokes are focal brain injuries that lead to measurable motor deficits depending on the site and extent of damage. Most assays that quantify post-stroke disability in preclinical models (particularly lateralized motor behavior) rely on labor-intensive manual scoring subject to significant inter-user variability. We therefore created a deep learning model to automate the quantification of post-stroke motor behavior. We used DeepLabCut, a neural network toolkit for rapidly building deep learning models, to track user-defined body parts. Using a modified residual network paradigm, these models achieve excellent performance with only 200 labeled training images. We then trained the model on non-injured mice. This model then extracts the Cartesian coordinates of four different body parts: the nose, both ears, and the base of the tail. A fifth point, the center of the head, is calculated afterward by finding the midpoint between the ears. We then derive the turning angle to quantify lateralized motor behavior. Next, mice underwent stereotaxic intrastriatal collagenase injection to model intracerebral hemorrhage. At 72 hours, behavior data was collected in an Open Field for 10 minutes at 25 fps., and the model was used to quantify lateralized behavior in injured vs naive mice. Videos were manually scored by observing rotational orientation changes; a 90-degree rotation counts as a left or right turn by direction. The right-to-left turn percentage is calculated for direct comparison with our paradigm. Our program was also compared to the gridwalk assay, a gold-standard test for lateralized motor deficits. Using these benchmarks, we evaluated performance in an initial cohort of four mice recorded before and after injury. Our workflow predicted the injury side with 100% accuracy and agreed with manual scoring in 87.5% of videos. Derived injury bias scores correlated with gridwalk performance, suggesting automated turning measurements capture functionally relevant deficits.We propose this model as an objective, consistent, and scalable method for quantifying post-stroke motor deficits in an automated way, which can serve as an efficient alternative to manual motor behavior scoring in preclinical stroke models.

Disclosures: L. Messe: None. **S. Santos:** None. **S. Reyes-Esteves:** None.

Poster

PSTR383: Data Analysis: Software Tools I

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Program #/Poster #: PSTR383.29/LL96

Topic: J.07. Data Analysis and Statistics

Title: Scalable Cellular-Level Multi-Marker Colocalization in Whole-Brain Light-Sheet Datasets

Authors: J. ZEITOUN[1], A. REKSOATMODJO[1], **C. REDD**[1], B. PEKAREK[2], R. AZEVEDO[3], *N. GUANZON[1], S. P. GANDHI[3], D. G. WHEELER[1,4], P. CHEUNG[1];
[1]Translucence Biosystems, Irvine, CA; [2]Res., Pekarek Lab., Berkeley, CA; [3]Neurobio. and Behavior, Univ. of California, Irvine, CA; [4]Activity Signaling, LLC, San Diego, CA

Abstract: Despite major advances in tissue labeling and imaging technologies, imaging more than a few hundred microns into tissue has historically required sectioning and mounting thin tissue slices on glass slides. When studying genetic or pharmacological manipulations that may affect the entire brain, this region-focused approach can limit discovery by restricting analysis to predefined areas of interest. Tissue clearing and light-sheet microscopy overcome these limitations by enabling intact-brain imaging and providing comprehensive, unbiased anatomical and functional insights. However, the value of these approaches ultimately depends on the tools available to analyze the resulting terabyte-scale datasets. Recent advances in multiplexed labeling and whole-brain imaging now enable simultaneous visualization of multiple markers throughout intact tissue volumes. Yet quantifying spatial relationships among labeled populations remains challenging due to dataset size, variability in segmentation outputs, and the need to distinguish biologically meaningful associations from random spatial proximity. Robust and reproducible methods for large-scale colocalization analysis are therefore essential for interpreting multi-marker imaging experiments. Here, we present newly developed tools for quantifying the cellular colocalization of cFos and Npas4, two immediate-early gene (IEG) products whose expression is differentially regulated by external stimuli. These methods are also applicable to therapeutic discovery workflows, including quantification of antibody-based therapeutics relative to their targets, such as amyloid plaques. The workflows support both overlap-based and distance-based colocalization analyses, enabling quantification of marker co-expression, cellular proximity, and region-specific interactions. They generate object-level and region-level metrics while maintaining reproducibility across studies and computational environments. Together, these tools provide a scalable and reproducible framework for large-scale colocalization analysis, enabling biologically meaningful interpretation of multi-marker whole-brain imaging datasets.

Disclosures: J. Zeitoun: None. **A. Reksoatmodjo:** None. **C. Redd:** None. **B. Pekarek:** None. **R. Azevedo:** None. **N. Guanzon:** None. **S.P. Gandhi:** None. **D.G. Wheeler:** None. **P. Cheung:** None.